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RECENT ADVANCES IN OPIOID PHARMACOLOGY

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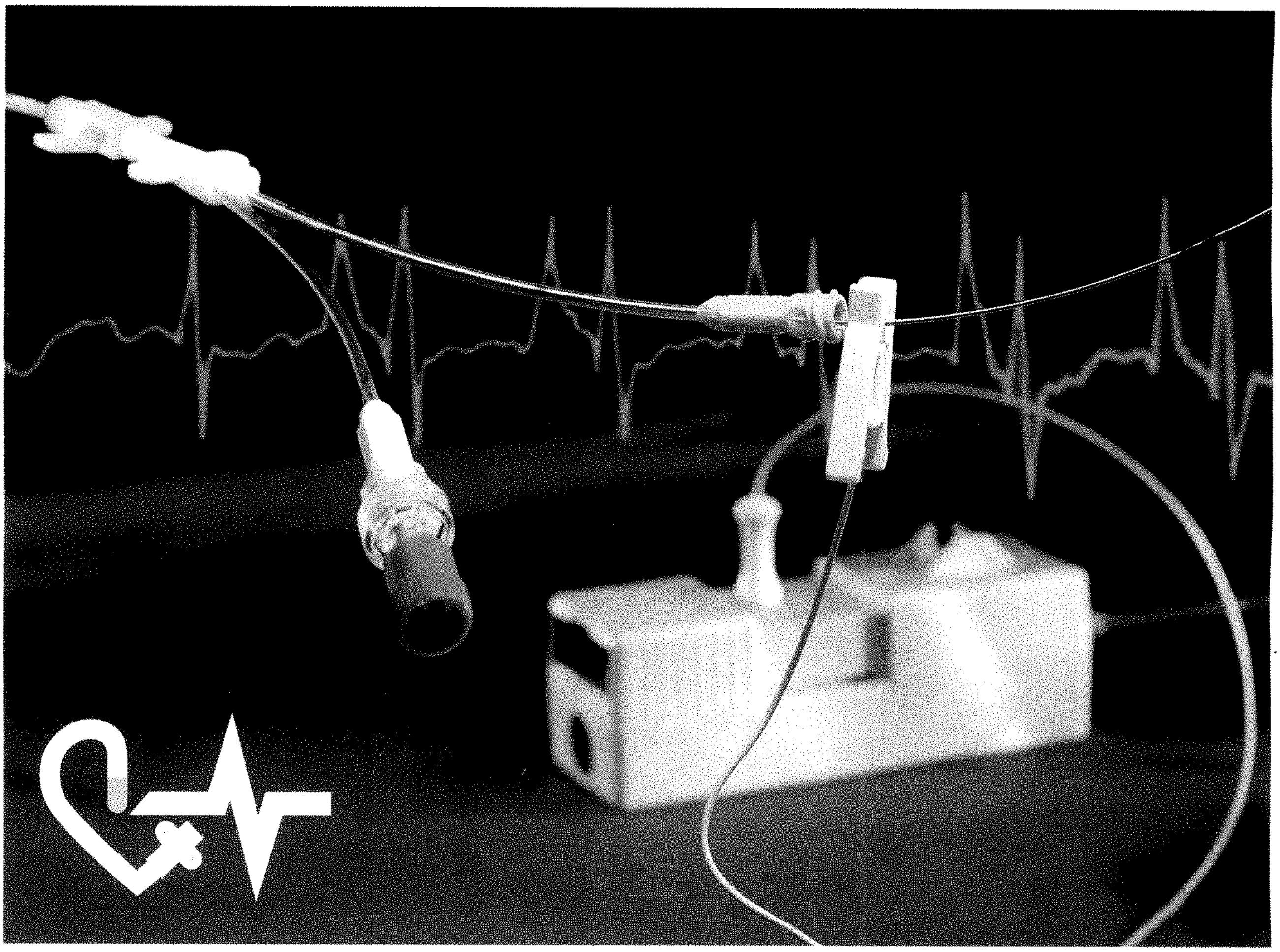

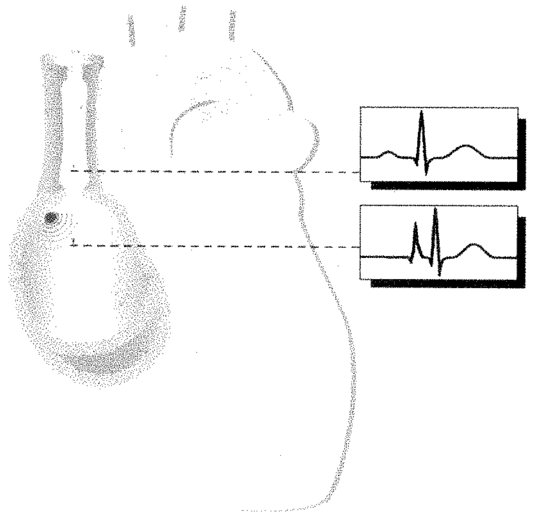

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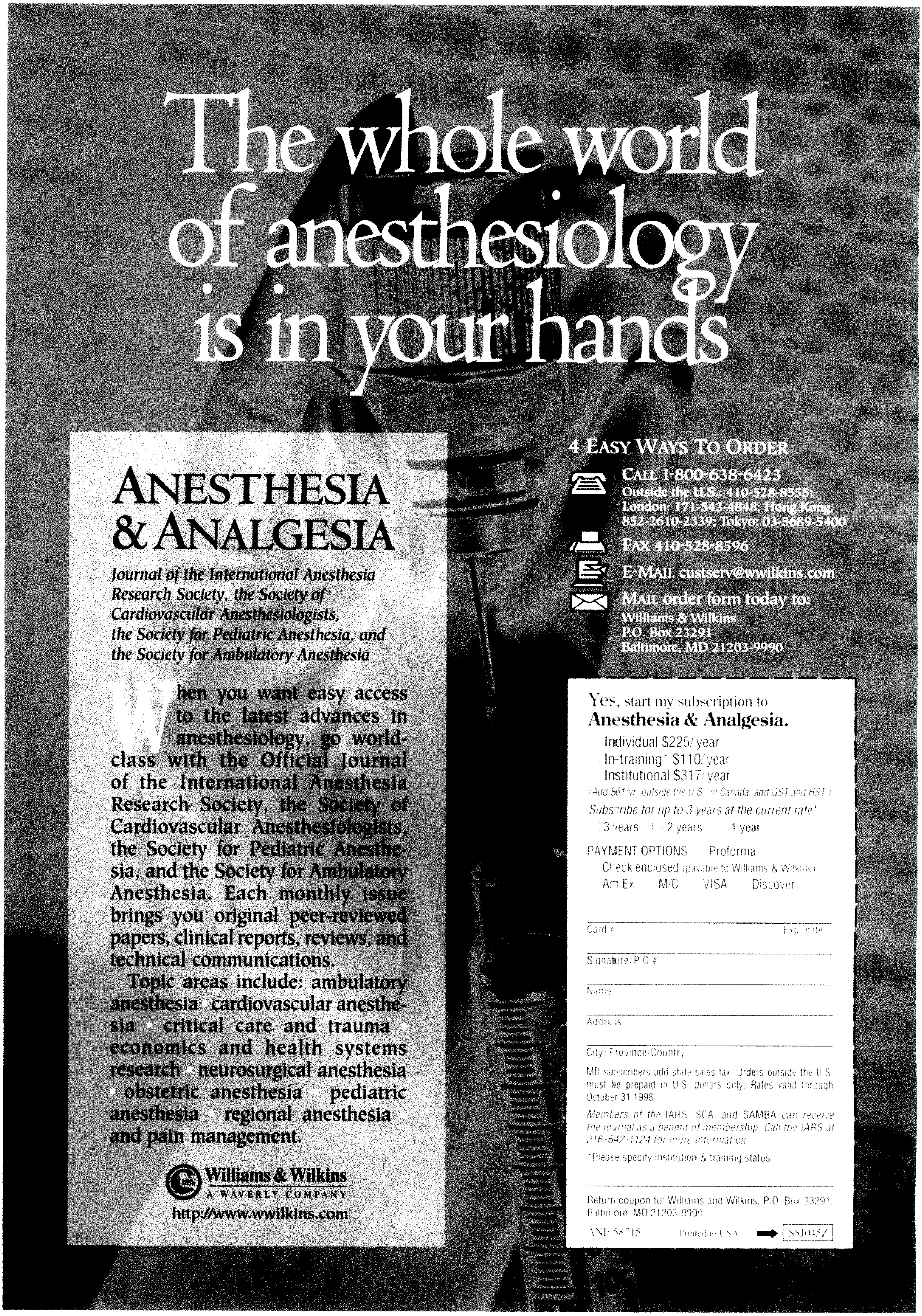

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Foreword

Perioperative anaemia is frequent and is associated with increased morbidity and mortality, especially in those patients with cardiovascular disease. In the past, treatment of anaemic patients would have involved transfusion of donor blood, but current attitudes have altered, not least as a result of the HIV epidemic, leading to a radical change in transfusion practice. The risk of transmission of viral diseases by allogeneic blood transfusion has been reduced significantly by more extensive testing and preparation, and by using products manufactured by state of the art methods of gene technology. Also, to reduce the previous liberal use of blood and blood products, transfusion guidelines have been established by professional associations and health authorities in many countries. In addition to improvements in surgical technique, blood saving methods are now standard practice in perioperative medicine, so that more operations are possible without transfusion. However, the efficacy and cost effectiveness of blood saving methods have recently been questioned and initial enthusiastic use may have subjected patients to avoidable and unnecessary risks.

Simple transfusion of red cells may not necessarily improve outcome in anaemic patients. Remarkably low packed cell volume values can be well tolerated by surgical patients, with or without compromised circulatory function. In addition, the risk of anaemia from an underlying disease has to be distinguished carefully from the risk of anaemia caused by perioperative blood loss with optimal intraoperative and postoperative monitoring.

Within this framework doctors must establish treatments which are economically justifiable and advantageous for the individual patient. The international and multidisciplinary expert meeting "Perioperative Anaemia—Risk and Treatment" was organized by the Department of Anaesthesiology and Intensive Care of Graz (Austria) in March 1998 to discuss and highlight the problems associated with perioperative anaemia and strategies to manage these problems.

We hope that the studies and overviews published in this supplement of the *BJA* will be helpful in the appropriate management of anaemic surgical patients and allow improved outcome in these high-risk patients.

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Erythropoietic response to acute and chronic anaemia: focus on postoperative anaemia

C. E. VAN IPEREN, D. H. BIESMA, A. VAN DE WIEL AND J. J. M. MARX

Acute and chronic anaemia are common problems in medicine. Acute anaemia is usually caused by sudden blood loss as a result of trauma, surgery or other losses, for example in the gastrointestinal tract. Sepsis and acute inflammation may also cause acute anaemia. The most common cause of chronic anaemia is iron deficiency, followed by the anaemia of chronic disease (ACD).[1 2] ACD occurs in chronic and acute infectious and inflammatory disorders, and in neoplastic diseases.[1] Other forms of chronic anaemia are megaloblastic anaemia, haemolysis, anaemia associated with renal or endocrine failure and liver disease, disorders of haemoglobin synthesis, bone marrow failure, myeloproliferative diseases and other haematological malignancies.

Iron metabolism plays a key role in the process of erythropoiesis. Iron is an essential trace element and has a role in several biochemical processes such as oxidative phosphorylation in mitochondria. Total body iron content in a healthy human of 75 kg is approximately 4 g. Sixty percent (2.4 g) of this iron is found in the haemoglobin of circulating red cells.[3] Iron stores and iron availability for erythropoiesis can be assessed by various laboratory tests. Measurement of serum ferritin is correlated closely with the amount of body iron stores and has almost replaced the histological examination of bone marrow.[4] A serum ferritin value of less than 12 μg litre^{-1} reflects the absence of iron stores. Ferritin is a 24-subunit protein which can store up to 5000 iron atoms[5]; its production is regulated by iron at the translational level.[6] The iron supply to the erythroid marrow is reflected by measurements of serum iron and total iron binding capacity (TIBC) in addition to serum transferrin and transferrin saturation. Transferrin is a glycoprotein with a molecular weight of 80 kD and is capable of binding two iron (III) ions.[7] It is essential for the distribution of iron. TIBC is the total binding sites of all transferrin in the circulation. If the iron supply decreases, serum iron and transferrin saturation decline, while TIBC and serum transferrin concentrations increase. Iron can only be internalized by cells if bound to transferrin following interaction with the transferrin receptor.[7] The transferrin receptor consists of two identical polypeptide chains with a molecular weight of 90 kD each. Transferrin receptors are found in highest concentration on erythroid precursor cells and in the placenta.[7] In iron deficiency, transferrin receptors in plasma are increased and this reflects the increased density of surface transferrin receptors on iron deprived cells.[8 9] Furthermore, there is a close relationship between the amount of serum transferrin receptors and the rate of erythropoiesis.[8]

If iron is deficient in the developing erythrocyte, the terminal reaction in the haem biosynthetic pathway (chelation of the ferrous ion by protoporphyrin) becomes impaired. The catalysing enzyme, ferrochelatase, chelates zinc instead of iron, thus producing zincprotoporphyrin (ZPP).[10] This is a nonfunctioning entity and can be measured readily by fluorometry. Increased ZPP reflects a state of intracellular iron deficiency.[10 11] Increased ZPP values are also found in lead intoxication, anaemia of chronic inflammation and myelodysplasia.[11] Free erythrocyte porphyrins (FEP) are the same metabolites that accumulate intracellularly in an iron deficient state and are measured when an acid extraction step in the analysis converts ZPP to metal-free erythrocyte protoporphyrin.[12]

Erythropoiesis is under hormonal control by the glycoprotein erythropoietin (EPO). EPO has a molecular weight of 34 kD and is produced mainly in the peritubular cells of the cortex and outer medulla of the kidney.[13] The liver is the other site of EPO synthesis, contributing 10–15% to total EPO production, while in the fetus, the liver is the most important source of EPO.[13] EPO acts on the two specific erythroid progenitor cells: the burst forming unit erythroid (BFU-E) and the colony forming unit erythroid (CFU-E) which are derived from the pluripotent haematopoietic stem cell.[14] BFU-E, the earliest erythroid progenitor, is dependent on EPO for proliferation and maturation, and on other haematopoietic growth factors such as interleukin-3 and granulocyte–monocyte colony stimulating factor.[13 14] The late progenitor CFU-E depends only on EPO and gives rise to erythroblast colonies in approximately 7 days.[15] EPO may also affect the megakaryocyte cell lineage, resulting in an increase in marrow megakaryocytic colony forming units and an increase in platelet count.[13] The primary stimulus for EPO production is hypoxia and a reduced red cell mass (by a lowered haemoglobin concentration and

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oxygen transport). Normally, there is an inverse correlation between haemoglobin and EPO concentration: if haemoglobin concentration decreases, EPO values increase. In some diseases such as rheumatoid arthritis, cancer and AIDS, a blunted EPO response to anaemia is found.[2 16 17] Therefore, EPO concentrations are lower than in patients who are equally anaemic without these disorders. In chronic renal failure, the principal cause of anaemia is inadequate production of EPO by the kidney.[18]

Inflammation may interfere with erythropoiesis in several ways. Iron metabolism may be impaired via block in release of iron from the activated mononuclear phagocytic system.[19] Moreover, ferritin production may be increased in inflammation as a result of activation of translation of the ferritin mRNA by interleukin-1 (IL-1), a cytokine produced by activated macrophages and T- and B-lymphocytes.[20 21] Increased ferritin may lead to iron sequestration. Several cytokines, such as tumour necrosis factor α (TNF-α), β-interferon (β-IFN), γ-interferon (γ-IFN) and IL-1 may inhibit erythroid progenitors in a direct or indirect manner.[2] Interleukin-6 (IL-6), released by monocytes, T-lymphocytes, fibroblasts and endothelial cells during inflammatory responses, has a stimulating rather than a depressant effect on erythropoiesis.[2] However, anaemia is found in patients receiving recombinant human IL-6 and appears to be caused by dilution (an increase in plasma volume).[22 23] Cytokines produced during inflammation may also inhibit EPO production, resulting in the "blunted" EPO response. This seems particularly common with IL-1 and TNF-α. Finally, EPO action on the erythroid progenitors seems to be impaired by β-IFN, γ-IFN and TNF-α, probably via interaction with the EPO receptor. This inhibitory effect can be overcome by pharmacological doses of recombinant human EPO (rhuEPO).

Acute and chronic anaemia are discussed below, with special attention to postoperative anaemia.

Acute anaemia

Acute anaemia by blood loss occurs, for example, in blood donor populations and in patients involved in an autologous blood donation programme. Donation of 1 unit of blood (450 ml) results in loss of approximately 250 mg of iron in males and 210 mg iron in females (respectively 6% and 9% of total body iron).[24] Finch and colleagues found that donation of 1 unit of blood a year resulted in a 50% reduction in serum ferritin concentration in male blood donors.[24] With increased frequency of blood donations (up to three a year) the number of iron deficient donors (serum ferritin <12 μg litre^{-1}) increased to 13% in the male and 27% in the female donor group.[24] Repeated phlebotomy is compensated by increased production of erythoid marrow. This increase is dependent largely on the available iron supply, and may increase to 4–8 times normal.[25] Kickler and Spivak found a lack of EPO response to repeated phlebotomies in autologous blood donors.[26] Despite a decrease in packed cell volume from 0.42 to 0.36 in men donating blood with a 3-day interval, EPO concentrations increased only from 13 to 23 iu litre^{-1}, remaining below the upper limit of normal. This degree of anaemia is apparently not sufficient to increase EPO production adequately. Phlebotomy-induced anaemia in autologous blood donors can be corrected by rhuEPO.[27] Anaemia of acute inflammation and sepsis can be considered as an acute variant of the anaemia of chronic disease (ACD) and is not discussed extensively here.

Chronic anaemia

Iron deficiency anaemia is the most common form of chronic anaemia. Iron deficiency eventually gives rise to a microcytic, hypochromic anaemia. Iron depletion is recognized by an isolated low serum ferritin concentration (<12 μg litre^{-1}), while normal haemoglobin concentrations are still present. Progression to iron deficient erythropoiesis is characterized by an additional decrease in plasma iron and transferrin saturation, and increase in FEP or ZPP, but still no decrease in haemoglobin concentration. The next stage is iron deficiency anaemia. Causes of iron deficiency are grouped into physiological iron losses (e.g. menstruation), pathological iron losses (e.g. gastrointestinal bleeding), increased iron use (e.g. growth spurt) and decreased iron intake (e.g. diet, malabsorption).[28] Oral and sometimes i.m. or i.v. iron replacement therapy may be needed, after the cause of the iron deficiency anaemia has been established. EPO reponse in iron deficiency anaemia is inversely correlated with the degree of anaemia and is not impaired.

ACD is the second most common chronic anaemia and is usually a mild to moderate normocytic, normochromic anaemia. It is characterized by a low serum iron concentration, transferrin saturation and serum transferrin concentration and high serum ferritin concentrations.[1 2] Serum transferrin receptor concentration is usually normal, and these receptor values may help to distinguish between ACD and iron deficiency anaemia.[9] Several mechanisms play a role in the pathogenesis of ACD, such as shortened red cell survival, inhibition of marrow erythropoiesis, inhibition of EPO production and action, and altered iron metabolism, leading to hypoferraemia in the presence of adequate iron stores. These last three mechanisms are caused by inflammation as a result of the underlying disease, as discussed previously. ACD improves if the underlying disease is treated adequately.[1 2] The relative EPO deficiency found in patients with ACD and rheumatoid arthritis,[29] cancer[30] and AIDS with zidovudine therapy has led to the succesful use of rhuEPO in these patients.[31]

Anaemia in patients with chronic renal failure is caused mainly by a relative or absolute EPO deficiency, but iron deficiency, gastrointestinal blood loss, decreased survival of red blood cells, bone marrow fibrosis and aluminium intoxication may also contribute to anaemia.[18] The use of rhuEPO is well established in patients with end-stage renal disease on dialysis, and pre-dialysis patients also benefit from rhuEPO.[32 33] Packed cell volume values in these patients were significantly higher after 2 weeks of therapy with rhuEPO 150 iu kg^{-1} three times a week. A special problem in this category of patients is the possibility of a "functional" iron deficiency, which means normal iron stores but an inadequate iron supply to the bone marrow.[34] Iron supplementation is often needed to ensure an adequate iron supply for the increased erythropoietic rate. A discussion of the other causes of chronic anaemia is beyond the scope of this article.

Postoperative anaemia

Anaemia is common after major surgery and seems easily explained by blood loss during and after surgery. However, the characteristics of iron deficiency anaemia and phlebotomized healthy individuals (reduced serum iron and ferritin concentration, reduced transferrin saturation and increased serum transferrin and transferrin receptor concentration) are not found after major surgery. In the study of Biesma and co-workers, patients who underwent total hip surgery were followed for up to 42 days after surgery.[35] Variables in erythropoiesis, iron metabolism and inflammation were measured on several postoperative days. Decreased serum iron, serum transferrin and transferrin saturation were found, together with a two-fold increase in serum ferritin concentration, while serum transferrin receptor values remained normal. Haemoglobin concentration remained low for 2 weeks after surgery with only a mild increase in EPO concentration and reticulocyte count, not sufficient to increase the haemoglobin concentration in the first weeks after surgery. A marked inflammatory effect of surgery was found, as shown by increased concentrations of IL-6 and C-reactive protein, as found by others.[36–39] Four to six weeks after surgery, iron metabolism had returned to normal and haemoglobin concentration was nearly restored. In this phase, serum transferrin receptor was initially increased, indicating increased erythropoiesis, while iron was more available, as indicated by an increase in serum iron and transferrin saturation. No difference in erythropoietic response was found in transfused or non-transfused patients. Furthermore, iron supplementation had no effect on postoperative haemoglobin concentration or iron variables.

Postoperative erythropoiesis was compared in minor and major surgery by van Iperen and colleagues.[40] Blood loss was eliminated in the minor surgery group, giving a clearer view of postoperative erythropoiesis. Minor surgery (e.g. correction of hallux valgus, removing of exostosis) appeared to induce a state of hypoferraemia in the presence of adequate iron stores and a marked acute phase response. Despite the absence of blood loss, there was a slight, although significant, decrease in haemoglobin concentration for some weeks after surgery. This confirms the hypothesis that postoperative anaemia is caused not only by blood loss but also by the inflammatory effect of surgery which contributes to the persistence of anaemia. This ACD-like inflammatory anaemia after surgery might be considered a physiological event. High plasma and tissue iron concentrations may be unfavourable, as these can promote bacterial growth.[41] Furthermore, a low packed cell volume may be favourable from a rheological point of view, thus leading to less thromboembolic events after operation. Clinical studies have shown that iron supplementation during the first 2–3 weeks after surgery is ineffective.[35 42] Iron is stored in the mononuclear phagocytic system (MPS) during inflammation and is not readily available for erythropoiesis. A decrease in intestinal iron absorption, as observed in patients with ACD, may add to this ineffectiveness of oral iron supplementation.[43] Following the inflammatory period after surgery, oral iron may be supplementary to the iron released from the MPS.

RhuEPO may be just as effective in the correction of postoperative anaemia as it is in the ACD of rheumatoid arthritis and cancer. Indeed, a recent study by Green and colleagues showed a more rapid improvement in haemoglobin concentration in an 8-week study with rhuEPO compared with placebo, which started 2 weeks after orthopaedic surgery.[44] However, there was no difference in functional improvement between the two groups. Restoration of haemoglobin concentration in this group may have come too late. Starting rhuEPO therapy earlier may be more beneficial, perhaps before operation. Furthermore, an autologous blood donation programme facilitated by the use of rhuEPO may lead to higher pre- and postoperative haemoglobin concentrations.[27]

In summary, postoperative anaemia may be considered an acute variant of the anaemia of chronic disease because of the inflammatory effect of surgery and this may have implications for its treatment.

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Immune response and iron metabolism

G. Weiss, B. Widner, H. Zoller, W. Schobersberger and D. Fuchs

Iron and erythropoiesis

In vertebrates, haemoglobin is the most important oxygen transporting protein. It is a tetramer composed of two pairs of polypeptide chains and four haem groups, and is present in a 34% solution in red blood cells.[1] The iron content of haemoglobin is 0.334%, and haemoglobin thus contains approximately 80% of total body iron in the normal situation. Consequently, iron metabolism has a significant impact on biosynthesis of haemoglobin, at least by direct interaction of iron regulatory proteins (IRP) with an iron responsive element (IRE), which is a RNA stem loop structure within the 5'-UTR of eALAS mRNA, conferring translational regulation of this enzyme. Binding affinity of IRP to IRE is modulated by intracellular iron concentrations, oxidative stress and nitric oxide. Iron deprivation states and, in a similar manner increased nitric oxide and oxygen radical formation, result in increased affinity of IRP for e-ALAS IRE thus decreasing e-ALAS mRNA translation (for review see Klausner, Rouault and Harford[2] and Hentze and Kühn[3]). In contrast, high intracellular iron concentrations reduce IRE binding activity of IRP thus enhancing e-ALAS mRNA translation and subsequently haem biosynthesis. In addition to this direct relationship between iron supplementation and biosynthesis of haemoglobin, indirect effects also influence production of red blood cells.

Transferrin, a non-haem iron binding glycoprotein, is necessary for the transport of absorbed dietary iron. Approximately one-third of transferrin is complexed with iron (III). After resorption of iron from the small intestine, transferrin transports iron to iron-free apoferritin. Iron-containing ferritin is the most important iron-storage protein in mammals; one molecule may store more than 50 000 iron (II) atoms. Ferritin is found in the spleen, liver, bone marrow, tissue monocytes, macrophages and reticulocytes. Excess iron is stored intracellularly and can be mobilized when needed. Iron deficiency caused by nutrition is not only characterized by decreased iron and haemoglobin concentrations in blood but also by reduced concentrations of ferritin and of several other haem and iron containing proteins, whereas transferrin and soluble transferrin receptors are increased.

Iron and the immune system

Iron homeostasis is central in the regulation of immune function.[4] On the one hand, environmental iron depletion is part of the antimicrobial and cytocidal strategies of immunocompetent cells, limiting the growth of invading pathogens or tumour cells by withdrawing this essential element. On the other hand, iron is also essential for proliferation and differentiation of immune cells during the state of activation. Moreover, iron catalyses the formation of highly toxic hydroxyl radicals, thus contributing to the killing of intracellular pathogens in activated monocytes/macrophages.[5] As a consequence, a shift of iron from the environment into immune cells takes place during the immune response (fig. 1). Thus the decrease in metabolically available iron during the immune response is part of a strategy of macrophages directed to enhance their responsiveness to cytokines, especially to the action of interferon-γ. Small environmental iron concentrations upregulate cytokine-induced effects in macrophages.[4 6]

Iron and anaemia of chronic disease

Many chronic disorders are associated with the development of anaemia, especially in the later stages.[7 8] Anaemia often indicates a poor prognosis in malignant diseases, and in chronic infections such as intracellular bacteria (*M. tuberculosis*) or viruses (HIV infection). Patients with autoimmune diseases (e.g. systemic lupus erythematosus or rheumatoid arthritis) frequently develop chronic anaemia. These diseases are characterized by involvement of the cell-mediated immune system with activation of T-helper cells type 1 (Th1-cells), release of characteristic cytokines (e.g. interferon-γ and interleukin-2) and activation of monocytes/macrophages.

Iron metabolism is disturbed in the anaemia of chronic disease. Low serum iron concentrations are common. Serum transferrin concentrations and the iron saturation of transferrin are often decreased. In contrast, iron stores are increased, as reflected by increased ferritin concentrations. Activated monocytes/macrophages may cause hypoferraemia, although how iron is shifted from the circulation into storage sites is not yet understood.[4] Several cytokines may alter iron homeostasis in chronic inflammatory disorders. Cytokines derived from the Th-1 immune

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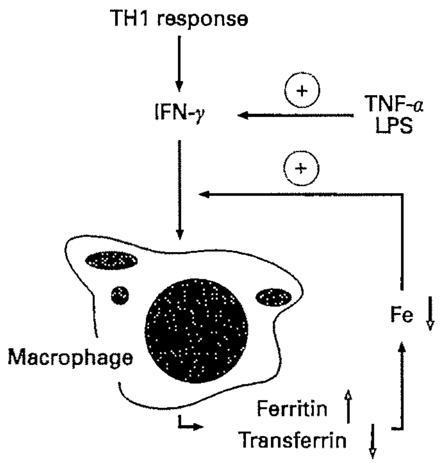

Figure 1 Scheme of the influence of cytokines such as interferon-γ (IFN-γ) released during the immune response on iron metabolism. TNF-α=tumour necrosis factor-α, LPS=lipopolysaccharide, Fe=iron.

branch or activated macrophages such as TNF-α, IL-1 or IL-6 may stimulate the transcription of ferritin (fig. 1) and thus cause hypoferraemia. Even Th-2 cytokines, such as IL-4 or IL-13, may disturb iron metabolism (for review see Weiss[9]). They mainly enhance transferrin–receptor expression and consequently iron uptake into macrophages, causing hypoferraemia (fig. 1). Some cytokines may have an indirect effect via the production of nitric oxide or reactive oxygen intermediates[4] (e.g. during cell-mediated (Th1-type) immune response) altering iron regulation by IRE/IRP interactions.[10 11]

Neopterin and cell-mediated (Th1-type) immune response

After activation with interferon-γ, human monocytes/macrophages produce and release large amounts of neopterin, a pyrazino-pyramidino compound which is characteristic for humans and primates. A cell-mediated immune response is reflected by increased neopterin concentrations in blood or urine *in vivo*.[12] Monitoring of neopterin concentrations is a sensitive method to detect early immunological complications such as rejection or infections in allograft recipients.[13] Increased neopterin concentrations are also common during infections with viruses (e.g. HIV infection, cytomegalovirus infection, Epstein–Barr virus infection), parasites (malaria) and intracellular bacteria (e.g. *M. tuberculosis*), in autoimmune diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis) and in certain types of cancer (e.g. haematological neoplasias, carcinoma of the bronchi, gynaecological tumours, prostate cancer[12–15]). In these disorders, neopterin concentrations and the degree of cellular immune activation parallels disease activity. Neopterin concentrations can predict the further course of the disease, especially in patients with human immunodeficiency virus (HIV) infection[16 17] and in patients with malignant diseases.[18]

Why activated monocytes/macrophages increase the production of neopterin is not yet fully understood. In earlier studies a close association was found between the capacity of activated monocytes/macrophages to release hydrogen peroxide and the amount of neopterin produced by the same cells.[19] From these data one may conclude that neopterin concentrations measured in patients indicate the state of oxidative stress caused by the activated immune system.[20] Neopterin derivatives can interact with reactive molecules such as reactive oxygen, chlorine and nitrogen intermediates. Oxidative stress mediated by such compounds can be enhanced by neopterin derivatives, as shown in chemiluminescence measurements and in bacterial cultures[21] and also in cell cultures. Neopterin derivatives mimic or enhance the effects of hydrogen peroxide, and induce programmed cell death (apoptosis[22 23]) or the expression of nuclear factor κB[24 25] and the nitric oxide gene[26] in human T-cell lines and in rat vascular smooth muscle cells. Neopterin may also suppress erythropoietin formation in the human hepatocytic cell line HepG2.[27]

Neopterin and iron metabolism

In patients with chronic disorders (e.g. HIV infection, bacterial infections, systemic lupus erythematosus or malignant diseases), neopterin concentrations correlate inversely with haemoglobin concentrations.[7] In cancer patients, neopterin concentrations are greatest in those types of tumour where patients have the greatest risk of anaemia. In patients with haematological neoplasias,[28] ovarian and cervical cancer,[29] anaemia and a high proportion of increased neopterin concentrations are both present, while in women with breast cancer, increased neopterin concentrations are rarely observed and the prevalence of anaemia is small.[30] Neopterin concentrations are also related to iron metabolism (fig. 2): patients with gynaecological cancer[29] and HIV infection[31] show significant inverse correlations between serum iron, transferrin and neopterin concentrations, and positive correlations were evident between ferritin and neopterin concentrations.[28–31] These data confirm the association between persistent activation of cell-mediated immunity in such patients and the shift of iron from the circulation into iron storage pools (see above).

Interferon-γ *in vitro* and *in vivo*

Patients with chronic diseases, such as advanced cancer and autoimmune and severe infectious diseases, have features of immunodeficiency rather than an activated immune system. Such patients are prone to secondary infections, especially of viral origin. Cell-mediated (Th1) immune deficiency could explain susceptibility. Cellular immune status was tested *in vitro* by the responsiveness of T-cells to antigenic or mitogenic stimulation. In addition to T-cell proliferation assays, cytokine production, mostly interferon-γ and interleukin-2, was measured in culture supernatants. T-cells were less able to respond to antigens with induced proliferation and cytokine production. Although interferon-γ was a potent inhibitor of erythroid progenitor cells,[32] the immunological results did not suggest that interferon-γ caused anaemia in patients with immunodeficiency.

It now appears that immunodeficiency is very often associated with a state of hyperimmune activation and may even result from exhaustion of immune cells.[33] High concentrations of cytokines, including

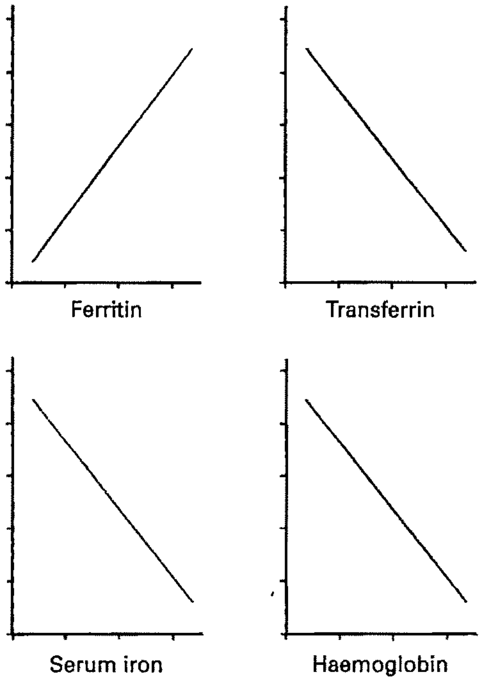

Figure 2 Scheme of the associations between immune activation phenomena and alterations of iron metabolism in patients with anaemia of chronic diseases.

interferon-γ, are very common in patients whose T-cells do not respond to antigenic stimulation in a correct way, shown by *in vitro* testing or skin test reactivity. The relationship between chronically stimulated immune cells and the development of immunodeficiency is best seen in patients with HIV infection where markers of immune activation such as neopterin and soluble tumour necrosis factor receptors are among the best predictors of disease progression[16,17,34] and an increase precedes the development of immunodeficiency.[35] Increased serum neopterin concentrations are closely associated with loss of *in vitro* responsiveness of T-cells. Loss of T-cell proliferative response and production of cytokines (e.g. interferon-γ), after antigenic stimulation is related to increased circulating concentrations of indicators of immune activation such as interferon-γ.

Conclusion

Immune activation and oxidative stress not only reduce the formation of erythropoietin but also inhibit erythroid precursor cells directly by reducing the response to erythropoietin. Th1- and Th2-derived cytokines depress iron handling in the anaemia of chronic disorders. This seems to be part of the strategy of the immune system to augment its action, since although iron reduces antimicrobial macrophage effector mechanisms, a shift of iron from the circulation into storage sites of the reticuloendothelial system deprives invading pathogens of this essential element and blocks their growth. If this is so, changes in iron metabolism will reverse as soon as the immune response is normalized.

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Myocardial ischaemia in anaemic patients

J. A. Wahr

Myocardial ischaemia and infarction are two of most significant perioperative complications that anaesthetists must prevent or treat. Mangano's review of the problem in 1990 stated that of the 25 million patients undergoing non-cardiac surgery each year in the USA, approximately one-third, or 8 million, are at risk of cardiac morbidity or mortality.[1] An anticipated perioperative infarction rate of 5% in patients with coronary artery disease would mean that 400 000 patients will suffer this adverse outcome each year. Clearly, adverse perioperative cardiac outcome poses a significant personal and health economic risk. More discouragingly, there are few reversible preoperative factors which are predictive of risk. For example, the most commonly cited risk factors for adverse cardiac outcomes are sex, age, urgency of operation and presence of existing congestive heart failure, diabetes or significant cerebral vascular occlusive disease.[2–4] Although these factors are easily identified, they cannot be changed perioperatively to decrease risk. One of the relatively few physical conditions which may contribute to myocardial ischaemia, and is also reversible, is anaemia. This discussion will address briefly the physiological basis for the association between anaemia and ischaemia, and review the existing literature on the subject.

Physiology

PATHOPHYSIOLOGY OF MYOCARDIAL ISCHAEMIA

Myocardial ischaemia occurs when oxygen delivery is insufficient to meet oxygen requirements. The determinants of myocardial oxygen demand are wall tension, heart rate and contractility. The determinants of myocardial oxygen delivery are arterial oxygen content and coronary arterial blood flow.

Although other tissues can compensate for less oxygen content or delivery by increasing the oxygen extraction ratio, the extraction ratio of the myocardium at rest is nearly 90% of that during exercise, and experimentally induced myocardial ischaemia causes only small increases in extraction of oxygen.[5] There is great reserve, however, in myocardial blood flow under normal conditions. In common with cerebral blood flow, myocardial blood flow is autoregulated between a mean arterial pressure of 60–120 mm Hg, with flow held constant over a wide range of perfusion pressures, as long as oxygen requirements remain stable.[5] Changes in coronary vascular resistance occur in response to changes in oxygen demand. When local oxygen requirements increase, coronary blood flow can increase many fold either to keep oxygen delivery constant as arterial content decreases, or to meet increased oxygen requirements (fig. 1). Stenotic coronary vessels, however, must dilate distal to the stenosis to maintain flow at resting levels. A critical stenosis (usually stated to be 70% stenosis) results in maximal dilatation distal to the stenosis at rest, causing loss of blood flow reserve.[5] In such a region, any increase in myocardial oxygen demand causes myocardial ischaemia, as flow at that point is pressure dependent. In addition, a wide variety of influences can result in diminished blood flow secondary to vasoconstriction. Vascular endothelium can respond to changes associated with surgical stress (catecholamines are not only vasoconstrictors, they also increase platelet "stickiness" and increase the risk of acute thrombotic events).

Patients without coronary artery disease, therefore, have a tremendous ability to compensate for decreases in coronary arterial oxygen content; patients with coronary artery disease have a limited ability to compensate for, or to tolerate, uncompensated decreases in myocardial oxygen delivery. As detailed later, there is little clinical evidence that allows prediction of the critical haemoglobin or packed cell volume at which ischaemia develops in any given patient.

PHYSIOLOGICAL RESPONSE TO ANAEMIA

An understanding of the physiological response to anaemia is also required to understand the implications of this state in the perioperative period. As the haemoglobin concentration decreases, cardiac output increases, primarily as a result of decreases in systemic vascular resistance.[6] Both chronic and acute anaemia in the form of normovolaemic haemodilution decrease systemic vascular resistance and increase stroke volume.[6] The greatest relative oxygen transport capacity occurs at a packed cell volume of 30–33% (fig. 2).[7] As haemoglobin concentration and oxygen content decrease further, an increase in heart rate preserves global oxygen delivery. These compensatory changes, however, require an increase in myocardial work and oxygen consumption at a time when myocardial oxygen delivery is decreased.[8]

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Keywords: complications, anaemia; complications, ischaemia; blood, haemodilution; heart, ischaemia

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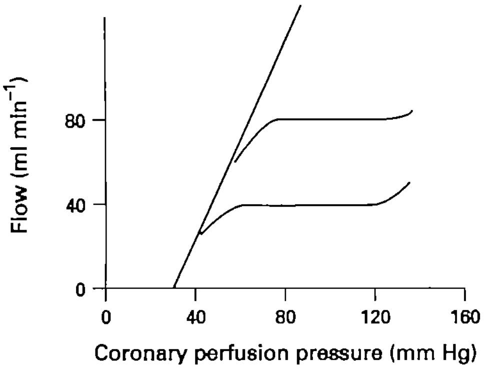

Figure 1 Coronary pressure–flow diagram demonstrating two autoregulation curves. Slanting straight line represents pressure–flow curve when the vessel is maximally dilated. Upper autoregulation curve demonstrates increased coronary flow at the same perfusion pressure as a result of increased oxygen demand or decreased oxygen delivery (anaemia). Reproduced with permission from Hoffman.[3]

In chronic anaemia, a secondary compensatory mechanism is an increase in 2,3 diphosphoglycerate (DPG), which shifts the oxygen dissociation curve to the right and increases oxygen release to the tissues. The primary focus of this review is the relationship between acute anaemia and myocardial ischaemia. It should be noted, however, that chronic anaemia and acute anaemia differ in compensatory mechanisms and in the risk of myocardial ischaemia. The greatest experience with chronic anaemia comes from patients with chronic renal failure. In these patients, haemoglobin concentration has been found to be predictive of left ventricular hypertrophy[9] but not of *de novo* ischaemic heart disease.[10] The relationship between chronic anaemia and cardiomyopathy in renal failure patients has led to recommendations for erythropoietin administration in these patients.[11]

Literature review

The data in the literature regarding the critical haemoglobin concentration at which myocardial ischaemia develops, or heart failure occurs, or at which mortality increases are divided into four types: (1) animal models without coronary or other physiological impairment; (2) healthy humans; (3) animal models with coronary artery stenosis; and (4) humans with either coronary artery disease or co-morbid conditions.

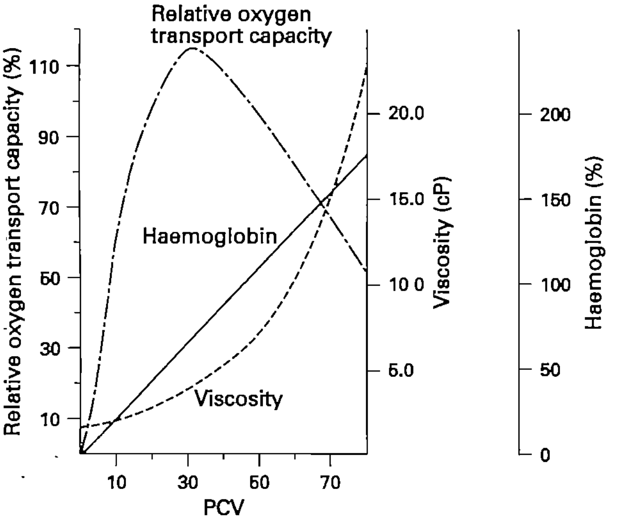

Figure 2 Influence of packed cell volume (PCV) on the relative oxygen transport capacity of blood. Note the increase in relative oxygen transport capacity as PCV decreases to approximately 30–33% despite the reduction in haemoglobin. Reprinted with permission from Wood and Kee.[7]

HEALTHY CONDITIONS

Animal models

In the absence of heart disease, animals demonstrate a tremendous ability to compensate for anaemia. Levy and colleagues reported cardiac failure in dogs at a mean packed cell volume of 9% (haemoglobin 3 g dl^{-1}),[12] as shown by a decrease in arterial pressure and an increase in left arterial pressure (fig. 3A). In the same experiment in dogs with a critical stenosis of the left anterior descending artery (LAD), cardiac failure occurred at a mean packed cell volume of 17% (fig. 3B).[12] Brazier and co-workers studied total and regional myocardial blood flow during haemodilution in dogs.[13] At moderate anaemia (haemoglobin 5–10 g dl^{-1}), total left ventricular blood flow increased from 82 to 106 ml 100 g^{-1}, and systemic oxygen delivery was maintained by increasing cardiac output 20% above control. The ratio of epicardial to subendocardial blood flow was not affected. However, during severe anaemia (<5 g dl^{-1}), total left ventricular flow increased to 150 ml 100 g^{-1}, and cardiac output increased to 50% above control values. This hyperdynamic state could not be maintained, myocardial blood flow was redistributed away from the subendocardium, myocardial ischaemia developed, cardiac output progressively declined and death occurred unless transfusion was initiated.[13]

Human studies

Little experimental data are available on the limits of anaemia in healthy humans. There are various case reports in the literature of extreme anaemia and the development of myocardial ischaemia, most often in Jehovah's Witness patients who refuse transfusion. In one adult patient, without coronary artery disease, recurrent myocardial ischaemia developed at a packed cell volume of 15% (lowest haemoglobin 4.8 g dl^{-1}).[14] In this patient, the episodes of myocardial ischaemia were treated successfully by slowing the heart rate with beta-blocking agents, and the patient was discharged on day 7 after operation. A similar case report of a healthy 84-yr-old Jehovah's Witness patient who experienced massive bleeding during tumour resection provides valuable information on the critical haemoglobin concentration at which oxygen consumption is limited by oxygen delivery.[15] The authors reported that at a packed cell volume of 8%, cardiac output was maintained at approximately 50% above preoperative levels. This patient survived for 12 h with a haemoglobin concentration of less than 3 g dl^{-1}. The authors did not report any measures of myocardial ischaemia.

In a study of 125 Jehovah's Witnesses undergoing surgery, both intraoperative blood loss and perioperative haemoglobin concentrations were found to be independent predictors of postoperative mortality (increasing from 6% at haemoglobin concentrations >8 g dl^{-1} to 61% at haemoglobin concentrations

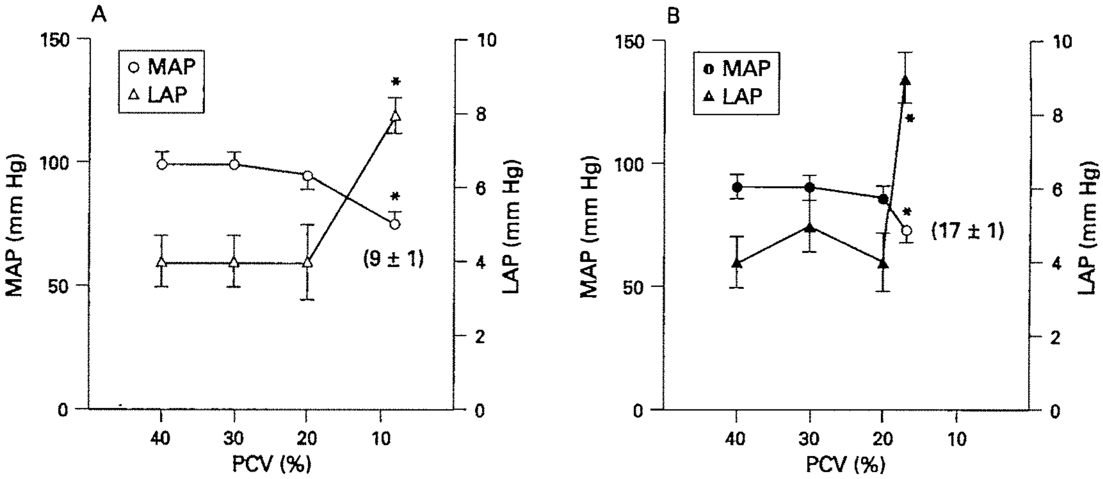

Figure 3 Comparison of changes in mean aortic pressure (MAP) and mean left atrial pressure (LAP) during graded haemodilution in control (A) and stenotic (B) dogs. Note that the criteria for cardiac failure were satisfied at packed cell volume (PCV) values of 9±1% in control and 17±1% in stenotic dogs Reprinted with permission from Levy and colleagues.[12]

<6 g dl^{-1}).[16] In children of Jehovah's Witnesses, haemoglobin concentrations of 3 g dl^{-1} were tolerated on cardiopulmonary bypass without difficulty.[17] A final study of the association between anaemia and mortality in Jehovah's Witnesses reported that blood loss >500 ml during surgery was a more important risk factor than preoperative haemoglobin concentration. Presumably, patients who tolerated a particular preoperative haemoglobin concentration continued to do well if further blood loss did not occur.[18]

In a study of haemodilution in elderly patients without known cardiac disease (age range 65–88 yr), normovolaemic haemodilution from a haemoglobin concentration of 11.6±0.4 to 8.8±0.3 g dl^{-1} was not associated with myocardial ischaemia or adverse cardiac outcome.[19] In all of these studies, it was either assumed or directly stated that normovolaemia was maintained.

ANAEMIA IN THE PRESENCE OF CORONARY ARTERY DISEASE OR CRITICAL ILLNESS

Animal models involving coronary artery stenosis

Most of the data on myocardial ischaemia and anaemia are from animal studies. In a study of haemodilution in anaesthetized, open chest dogs, Levy and colleagues showed that a critical stenosis of the LAD artery resulted in cardiac failure (low systemic artery pressure and increased pulmonary artery pressure) at a higher packed cell volume than in dogs without stenosis.[12] Cardiac failure occurred at a mean packed cell volume of 9±1 in control dogs and at 17±1% in dogs with stenosis ($P<0.05$) (fig. 3A, B). In contrast with control dogs, dogs with a stenosis of the LAD did not demonstrate an increase in blood flow in response to haemodilution, resulting in reductions in myocardial oxygen supply, and consequent decreases in lactate extraction and the endocardial:epicardial blood flow ratio. In both groups, myocardial oxygen extraction did not change with haemodilution.[12]

Hagl and colleagues studied dogs with a critical stenosis of the LAD and unaffected circumflex arteries and found that coronary blood flow increased nearly three-fold in the normal region, but was unchanged in the affected LAD region during haemodilution from a packed cell volume of 45% to as low as 15% (fig. 4).[20] In the affected LAD region, the velocity of shortening and contraction amplitude of the myocardium were reduced markedly compared with the control region.

In a similar study, Spahn and colleagues reported mild decreases in function (systolic shortening) in myocardium supplied by a critically stenotic LAD at a packed cell volume of 24±0.1%, and severe dysfunction at a packed cell volume of 14.0±0.1%.[21] In a further study, the same authors demonstrated that cardiac failure occurred earlier during haemodilution in dogs with multiple coronary artery stenosis (LAD and circumflex arteries) than in dogs with only one stenotic artery.[22]

In nearly all of these studies, the packed cell volume at which cardiac failure occurred in the presence of coronary artery stenosis was reported as the mean of several experimental animals. The lowest value at which all animals with coronary artery stenosis continued to have normal cardiac function was less often reported. In one study, 25% of the

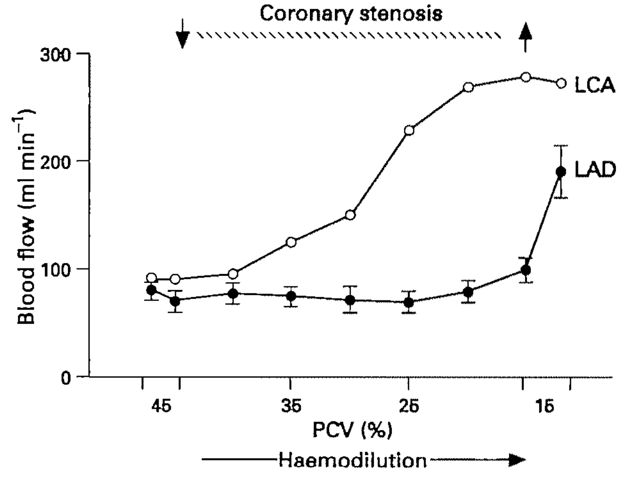

Figure 4 Comparison of the influence of isovolumic haemodilution (PCV%) on coronary flow in an intact left circumflex artery (LCA) and in a mechanically stenotic left anterior descending artery (LAD). No increase in coronary blood flow was seen in the compromised LAD until the mechanical stenosis was removed at a PCV of 15%. Reprinted from Hagl and colleagues.[20]

animals with coronary artery stenosis experienced some degree of cardiac failure at a packed cell volume as high as 27%.[21]

Human studies

The threshold packed cell volume for development of myocardial ischaemia, or worse, cardiac failure, is less well characterized in humans. Jalonen and colleagues studied myocardial oxygen balance (arterial–coronary sinus) and lactate in patients presenting for coronary artery revascularization.[23] Patients randomized to haemodilution were haemodiluted to 32% before cardiopulmonary bypass, with a resulting packed cell volume of 15% at the beginning of bypass (because of the crystalloid prime of the pump). Control patients, who were not haemodiluted, had a mean packed cell volume of 27% at the beginning of bypass. Preoperative haemodilution to 32% produced a decrease in coronary sinus oxygen saturation and tension, but no patient demonstrated lactate production. At the start of bypass, when packed cell volume decreased to 15%, coronary sinus oxygen saturation and tension decreased significantly from pre-bypass levels. Control patients showed an increase in coronary sinus oxygen saturation and tension at the start of bypass (packed cell volume 27%).The authors concluded that "...hemodilution to a packed cell volume of 15% produces myocardial ischemia in patients with a normothermic unloaded heart".[23]

Herregods and colleagues studied 15 patients with left main coronary artery stenosis undergoing coronary artery bypass graft surgery who underwent limited intentional normovolaemic haemodilution to a packed cell volume of 34%, while 15 control patients were not diluted.[24] ST segment changes occurred in three patients in each group, and were similar in severity and duration in both groups. Ninety patients undergoing coronary artery bypass graft surgery were studied by Spahn and colleagues and were allocated randomly to undergo haemodilution (n=30) or no haemodilution (n=30).[25] All patients were receiving beta-adrenergic blocking drugs. Mean haemoglobin concentration achieved in the haemodilution group was 9.9±0.2 g dl^{-1}, and no changes in ST segments were noted in either group. The authors concluded that haemodilution to a haemoglobin value of 9.9 g dl^{-1} was well tolerated and fully compensated in patients with coronary artery disease receiving beta-blocking drugs.[25]

In a study of 90 critically ill postoperative patients, Czer and Shoemaker reported a mortality of 68% in patients who were not transfused until packed cell volume reached 21%, compared with a mortality of 13% in patients who were transfused at a packed cell volume of 27–33%.[26] At a pre-transfusion packed cell volume of less than 27%, there was an inverse correlation between pre-transfusion packed cell volume and improvement in oxygen consumption (the lower the packed cell volume, the greater the improvement in oxygen consumption).[26]

In a study of 4470 critically ill patients, survivors were found to have significantly higher haemoglobin values than those who died (10.4±2.3 *vs* 9.5±2.6 g dl^{-1}; P<0.0001).[27] In a subgroup of patients with cardiac disease, increasing haemoglobin values in anaemic patients were associated with improved survival (odds ratio=0.80 for each 1 g dl^{-1} increase; P=0.012). The authors concluded that anaemia increased the risk of death in critically ill patients with cardiac disease.[27]

Conversely, Carson and co-workers reported that the 30-day mortality in 8787 hip fracture patients was not influenced by perioperative transfusion if haemoglobin concentrations were 8.0 g dl^{-1} or higher.[28] At haemoglobin concentrations of 8.0 g dl^{-1} or lower, 90.5% of patients received a transfusion, which precluded further analysis of the association between anaemia and mortality in this elderly population. The full data from this study are shown in table 1.

Perhaps the most compelling evidence for preservation of packed cell volume in patients with coronary artery disease is a study by Nelson, Fleisher and Rosenbaum.[29] Twenty-seven patients undergoing infra-inguinal arterial bypass procedures were monitored continuously by ambulatory electrocardiographic recorders from the evening before surgery for up to 80 h after operation. Episodes of ischaemia were quantified, and morbid cardiac events such as death, myocardial infarction, unstable angina and ischaemic pulmonary oedema were analysed using receiver operating curves. A packed cell volume of 28% was identified as the threshold for morbid cardiac events. Of the 27 patients enrolled, 13 had a postoperative packed cell volume <28%. Ten of these 13 experienced myocardial ischaemia, and six sustained an adverse cardiac outcome. Of the 14 patients with a packed cell volume greater than 28%, only two experienced myocardial ischaemia, and no patient had an adverse cardiac outcome (fig. 5). The authors noted that patients with anaemia were significantly older and had longer intraoperative times; neither of these factors was found to correlate with adverse cardiac outcome. Although this study was limited by the small sample size and the case-control nature of the study, it supports maintenance of a higher packed cell volume in patients with risk factors for cardiac disease. Definitive evidence that maintenance of a haemoglobin concentration of 9–10 g dl^{-1} prevents occurrence of morbid cardiac events is lacking, and would require a prospective, randomized study.

In a recent review of the evidence for and against commonly recognized transfusion "triggers", Lundsgaard-Hansen concluded that tremendous variations exist between patients in oxygen delivery, extraction, and myocardial reserve, and that "for [these] reason[s], the critical haemoglobin is an

Table 1 Postoperative haemoglobin trigger and 30-day mortality Reprinted from Carson and colleagues[28]

	Transfused		Non-transfused	
Trigger haemoglobin (g dl^{-1})	No	Mortality (No. (%))	No.	Mortality (No. (%))
< 7.0	204	16 (7.8)	10	3 (30.0)
7.0–7.9	810	44 (5.4)	96	5(5.2)
8.0–8.9	1620	78 (4.8)	623	22 (3 5)
9.0–9.9	854	49 (5.8)	1355	61 (4.5)
10.0–10 9	144	9 (6.3)	1429	59 (4.1)
11.0–11 9	47	1 (2.1)	941	40 (4.3)
≥12.0	20	0 (0.0)	634	15 (2.4)
Total	3699	197(5.3)	5088	205(4.0)

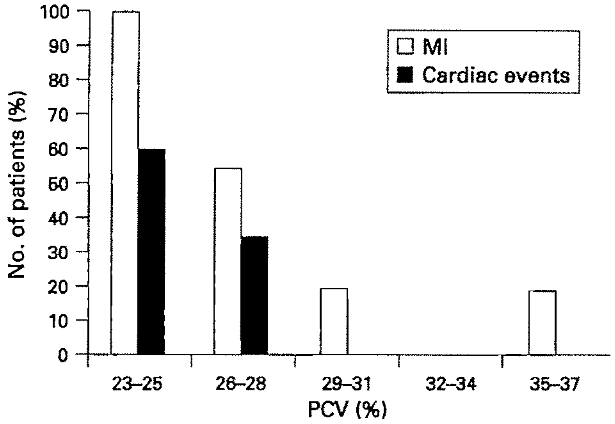

Figure 5 Incidence of myocardial ischaemia (MI) and morbid cardiac events as related to packed cell volume (PCV) in patients undergoing peripheral vascular surgery. Reprinted with permission from Nelson, Fleisher and Rosenbaum.[29]

individual value, and a generally valid 'transfusion trigger' does *not* exist".[30] Citing evidence that myocardial ischaemia is a critical factor in a patient's ability to tolerate anaemia, the author suggested that "patients over age 40 should not, as an elective procedure, be subjected to levels <10 gm/dL, without prior exclusion of silent myocardial ischaemia".[30]

Weighing the risks

The cited literature outlines the risks associated with allowing haemoglobin concentrations of less than 9–10 g dl^{-1} in patients with coronary artery disease or co-morbid conditions. However, there are risks inherent in transfusion of allogeneic blood also. How is a clinician to weigh the risks of transfusion *vs* not transfusing in a given patient? The difficulty of such decisions is increased by the level of uncertainty regarding the true incidence of adverse outcomes with either option. The decisive point in the perioperative patient with cardiac disease is most likely at a haemoglobin concentration of 9–10 g dl^{-1}. The data from Spahn and colleagues, Herregods and colleagues, and Jalonen and colleagues indicate that myocardial ischaemia does not occur when haemodilution, under otherwise controlled circumstances, results in a haemoglobin concentration greater than 9 g dl^{-1}.[22–24] Based on the study of Nelson, Fleisher and Rosenbaum, the decision not to transfuse despite a haemoglobin concentration less than 9 g dl^{-1} carries the risk of inducing myocardial ischaemia or a morbid cardiac event.[29] The decision to transfuse carries the risk of transmission of an infectious disease, whether bacterial or viral, the risk of a haemolytic reaction as a result of clerical error, and it is extremely rare and difficult to quantify outcomes such as immunomodulation. The recent incidences for contracting HIV or hepatitis C from an allogeneic transfusion (US data) are 1:493 000 and 1:103 000, respectively.[31] Hepatitis B still represents the highest risk at 1:63 000, and the aggregate risk has been calculated as 1 in 34 000. Using these values, the overall probability of an adverse outcome caused by transfusion of an allogeneic unit of red blood cells is not greater than 0.000029. That is, a patient undergoing surgery who receives transfusion of red blood cells to maintain a haemoglobin concentration greater than 9 g dl^{-1} has a 99.987% likelihood of *not* being exposed to an undetected infected unit. Although additional units increase the risk proportionately, the chance of an adverse outcome as a result of transfusion remains less than 1 in 10 000.

This risk of transfusing an infected unit must be weighed against the risk of experiencing an adverse outcome resulting from a haemoglobin concentration <9 g dl^{-1}. If the risks of morbidity stated by Nelson, Fleisher and Rosenbaum,[29] Czer and Shoemaker,[26] or Hébert and colleagues[27] are accurate, at least 40% of patients with significant cardiac disease who are not transfused will experience an adverse cardiac outcome. Accepting the limitations of these studies, and assuming that the true incidence of adverse outcomes is only half or one-third of that reported, the morbidity and mortality of anaemia remains much greater than the transfusion risks in patients with cardiac or other life-threatening diseases.

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Risk of allogeneic transfusions

M. M. Heiss

The clinical use of blood transfusions has opened new perspectives in surgery. However, it became apparent that blood transfusions were associated with risks, causing related morbidity and mortality. Initially, transmission of infectious diseases was of major concern. This diminished largely because of sophisticated donor blood testing which resulted in the reduction of transmission risk for hepatitis C to 1 in 1000 and HIV to 1 in 400 000.

Allogeneic blood transfusion is transplantation of foreign cells causing immunological reactions. As early as 1946 Medawar documented that alloreactive immunoresponses can be induced by transfusion; in transplantation surgery it was observed that blood transfusions can have measurable immunosuppressive effects. As this immunosuppression is potentially associated with every transfused allogeneic blood unit, it may of considerable importance. Therefore, the clinical consequences of the immunosuppressive, allogeneic blood effect on perioperative infection and tumour recurrence after curative resection should be considered seriously.

Blood transfusion-associated immunosuppression

Extensive experimental and clinical research has demonstrated multiple immunological effects.[1] However, the underlying mechanisms are still unclear. Many immunological effector systems have been shown to be altered[2] (table 1). There is no general consensus on whether or not these alterations are caused by blood transfusion itself or, in contrast, by factors related to the transfusion. Contradictory data have been found in prospective, randomized studies where blood transfusion was controlled by patients receiving immunologically neutral, autologous or leucocyte-depleted allogeneic blood transfusions.[3–6] Our data showed that cell-mediated immunity measured by deleted-type hypersensitivity responses was suppressed by allogeneic transfusions. Surprisingly an increased response was found in patients transfused with autologous blood.[3] Additional investigations on unspecific, cell-mediated immunity, as described by natural-killer and lymphokine-activated killer cell activity, substantiated the observations that autologous blood transfusion has an intrinsic immunomodulatory potential.[7] In the postoperative period, cellular immunity has been shown to be impaired as a result of surgical trauma. In this critical situation, additional suppression of cellular immunity by allogeneic blood transfusion may be pivotal.

Table 1 Blood transfusion-associated immunosuppression

Increased production of prostaglandin E_2[13]
Decreased release of interleukin-2[14]
Decreased production of TNF, IFN-γ, GM-CSF[15]
Decreased T4/T8 ratio[16]
Diminished NK cell activity[17]
Suppressed DTH reaction[18]
Reduced antigen presentation function by macrophages[19]
Unspecific suppressor cells[2]
Anti-idiotypic antibodies[20]
T-suppressor cells[21]
MLC blocking factors[29]
Donor-specific chimerism ("mixed chimerism")[30]

Clinical evidence for allogeneic blood transfusion-associated immunosuppression

The basic hypothesis is that blood transfusion-associated immunosuppression can be demonstrated clinically by its influence on postoperative infection rates and prognosis in resected cancer patients. As mentioned previously, it is difficult to analyse if blood transfusion itself is causing these clinical effects or if confounders of blood transfusions (e.g. blood loss, duration and difficulty of operation, tumour size or tumour stage) are responsible. Therefore, we and other investigators tried to resolve this issue by performing prospective, randomized studies in which patients undergoing resection of tumours were allocated randomly to receive either standard allogeneic transfusions or transfusions not associated with induction of a state of immunosuppression.[3–6] It has been documented that autologous blood transfusions do not lead to significant immunosuppression. Using this strategy it was possible to create two groups of patients who were comparable with regard to all tested variables that might influence the requirement for blood transfusion, risk of postoperative infection or risk of tumour recurrence. The differences observed should show the hypothetical clinical effect of allogeneic blood transfusion-associated immunosuppression.

Allogeneic transfusion and postoperative infection

In our study, we enrolled 120 patients with colorectal cancer and found a significant difference in postoper-

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ative infection rates.[3] Patients in the autologous blood group had an infection rate of 12% compared with 27% in the allogeneic blood group (odds ratio 2.75, 95% confidence interval (CI) 1.07–7.11; $P<0.05$). There was a clear association between blood transfusion modality and infection rate. A dose–response effect was seen; infection rates increased with the number of transfused blood units. Our conclusion was that allogeneic transfusions exhibited a significant dose-related risk of postoperative infection.

Numerous observational studies analysing the association between allogeneic transfusion and postoperative infection have been published.[1] In all studies using multivariate analysis, an independent and significant correlation was found in different clinical settings, such as open heart surgery, abdominal surgery or trauma patients. Prospective, randomized studies with control groups who had received either autologous or leucocyte-depleted blood largely replicated these results (table 2). In one multicentre study, the use of either leucocyte-depleted, allogeneic or buffy-coat-depleted allogeneic blood transfusion had no significant clinical effect.[5] The Dutch study comparing allogeneic and autologous blood found no significant differences, but an increased infection rate was seen with an increasing number of transfused units. The overall conclusion from the available data was that no other variable was more consistently associated with postoperative infection than perioperative allogeneic blood transfusion.

Allogeneic transfusion and prognosis in cancer surgery

The clinical relevance of the immunological risk of allogeneic transfusion enhancing tumour recurrence is highlighted by the fact that in Germany, more than 50% of all transfused allogeneic blood (more the 3 million units per year) are given during oncological surgery. Gantt speculated that it might be possible for patients with cancer resections who received allogeneic transfusions "to be suppressed to the point where the malignant tumour has a better chance to survive".[8] In our study, multivariate analysis of established risk factors for tumour recurrence, and surgery-related variables reflecting other potential immunosuppressive conditions, found that only pT-stage, pN-stage and the need for allogeneic transfusions (odds ratio 6.18, 95% CI 2.20–17.37; $P<0.001$) were independent predictors of prognosis.[9] A recent long-term analysis of tumour-free survival (median follow-up time 68 months) of both randomized study groups showed a shorter survival time in the allogeneic blood group (P corrected for pT and pN=0.067) (figs 1, 2). Subgroup analysis of patients where additional allogeneic transfusions in the autologous blood group were excluded, found this higher risk of tumour recurrence to reach significance ($P=0.047$). However, a similar study performed by the Rotterdam group using a multicentre approach was not able to detect a difference between patients allocated randomly to receive either allogeneic or autologous transfusions in colorectal cancer surgery.[4] Despite some methodological differences and questions concerning the study control group, the conflicting results after these two randomized studies are similar to those found after many retrospective observational studies. Large series demonstrating an independent and significant effect of allogeneic transfusions on long-term prognosis were contradicted by studies where such an association was not found. Two large meta-analyses tried to summarize the available literature on allogeneic transfusion and colorectal cancer surgery.[10 11] The analysis of Chung, Steinmetz and Gordon entailed 30 studies with more than 5000 patients and the overall odds ratio was significantly increased at 1.69 (95% CI 1.31–2.19).[10] The second analysis of Vamvakas and Moore examined data from 11 studies of colorectal cancer patients.[11] Again, in this study the relative risk was significantly increased at 1.37 (95% CI 1.20–1.56). However, even large meta-analyses are not able to answer the question of whether or not there is a causal association between allogeneic transfusions and worse outcome after cancer surgery.

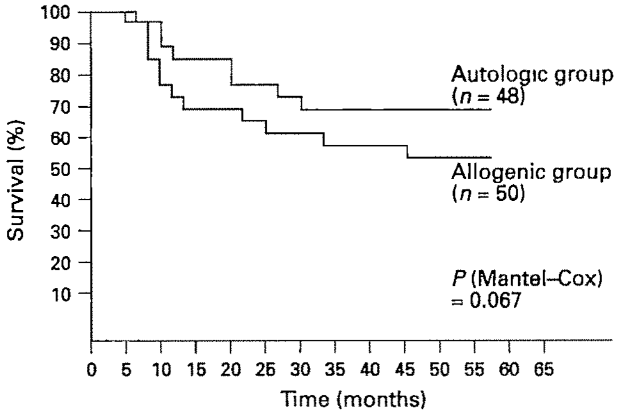

Figure 1 Tumour-free survival in all patients. Long-term tumour-free survival in all patients ($n=100$). Median follow-up=68 months (Kaplan–Meier method)

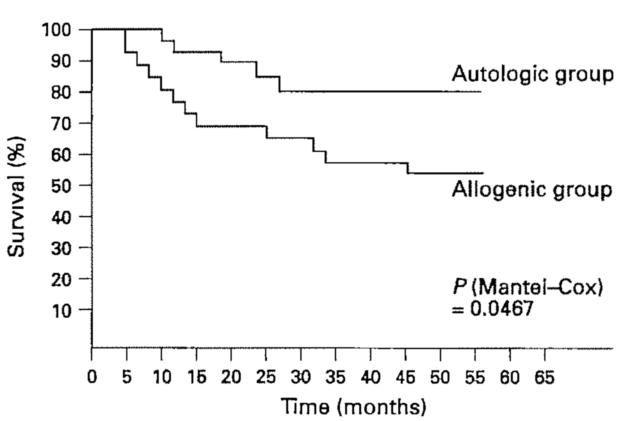

Figure 2 Tumour-free survival in a subgroup of patients. Long-term tumour-free survival in patients with blood loss of less than 1000 ml ($n=62$). Median follow-up=68 months (Kaplan–Meier method).

Conclusion

The currently available data demonstrate that there is a significant association between allogeneic transfusions and a higher postoperative infection risk. The underlying mechanism is most probably allogeneic blood transfusion-induced immunosuppression.

The association between allogeneic transfusion and worse long-term prognosis in cancer surgery is

Table 2 Comparison of the relationship between allogeneic blood transfusion and autologous blood transfusion (or leucocyte-depleted allogeneic blood) and the risk of postoperative infection. TEP=Hip prosthesis; ery. concn=erythrocyte concentrate; leucocyte-depl.=leucocyte-depletion; PCV=packed cell volume. **P* significant for blood transfusion, independent of blood modality (autologous or allogeneic)

	Study design	No. of patients	Type of surgery	Transf. freq. (%)	Transfusion product	Transfusion trigger	Postoperative infection rate	*P*
Murphy[22]	Retrospective ("case-control")	84	TEP	100	Ery. concn/ whole blood	–	3% autologous blood (n=34) 32% allogeneic blood (n=50)	0.0029
Triulzi[23]	Open prospective	109	Spinal surgery	–	Allog. ery. concn/ autol. ery. concn/ whole blood	–	20.8% allogeneic blood (n=24) 3.5% no allogeneic blood (n=85)	0.0160
Fernandez[24]	Retrospective	376	Orthopaedic surgery	32.4	Whole blood/ ery. concn	–	5% no blood (n=122) 5% autologous blood (n=140) 6.9% allogeneic blood (n=72) 11.9% autol./allogeneic blood (n=42)	0.0010
Jensen[25]*	Randomized	197	Colorectal cancer	52.8	Whole blood/ leucocyte-depl. whole blood	PCV <0.35 Hb<7.2 nmol litre^{-1}	2% without blood (n=93) 2% filtrated/allogeneic blood (n=48) 23% allogeneic blood (n=56)	<0.0100
Houbiers[5]*	Randomized	697	Colorectal cancer	64.0	Leucocyte-depl. ery. concn/ery. concn	–	35% filtration/allogeneic blood (n=337) 32% allogeneic blood (n=360)	0.0010
Vignali[26]	Open prospective	161	Colorectal cancer	53.0	Autol. whole blood allog. ery. concn/ whole blood	–	9% no blood (n=75) 14% autologous blood (n=36) 33% allogeneic blood (n=48)	<0.0050
Busch[27]	Randomized	475	Colorectal cancer	67.0	Autol.ery. concn/ allog. ery. concn	Hb <10.5; blood loss >500 ml	27% autologous blood (n=236) 25% allogeneic blood (n=239)	<0.0010*
Heiss[9]	Randomized	120	Colorectal cancer	75.0	Autol. ery. concn/ allog. ery. concn	Hb <10.0	12% autologous blood (n=58) 27% allogeneic blood (n=62)	0.0470
Jensen[28]	Randomized	589	Colorectal cancer	44.1	Leucocyte-depl. ery./ery. concn	PCV <0.70 Hb <7.0 nmol litre^{-1}	11.4% filtered/allogeneic blood (n=290) 30.1% allogeneic (n=299)	<0.05

unclear. However, most studies have demonstrated a correlation between tumour recurrence and allogeneic transfusion. A potential connection between the perioperative, immunosuppressive, allogeneic transfusion effect and long-term prognosis is probably its impact on minimal residual disease still remaining after curative tumour resection. This effect may condition the patient for the establishment of disseminated tumour cells and metastatic systemic disease.[12]

It is important to point out that in light of these data, the clinical effects of allogeneic transfusion-associated immunosuppression can be relevant clinically. Therefore, avoidance of allogeneic blood transfusion is beneficial, especially in oncological surgery.

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Perioperative management of anaemia

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Most of the millions of units of red blood cells transfused annually in the USA are given to surgical patients.[1-3] In theory, perioperative anaemia may lead to mortality, morbidity and functional impairment through inadequate oxygen delivery to tissues. Clinicians transfuse anaemic surgical patients with red cells in the hope of preventing adverse outcomes by restoring oxygen-carrying capacity. Although blood transfusion safety has improved dramatically in recent years, it is not entirely risk free. The decision to administer red cells in the perioperative setting thus hinges on the risks of anaemia, the efficacy and effectiveness of transfusion in ameliorating these risks, and the risks of transfusion. The risks of anaemia may in turn vary for individual patients depending on their medical problems, age, amount of blood loss and symptoms.

There have been many guidelines on red cell transfusion. The American Society of Anesthesiologists Task Force on Blood Component Therapy published the most recent ones in 1996.[4] After an evidence-based review of the medical literature up to mid-1994, the Task Force developed the following recommendations:

(1) Transfusion is rarely indicated when haemoglobin concentration is greater than 10 g dl^{-1} and is almost always indicated when it is less than 6 g dl^{-1}, especially when the anaemia is acute.

(2) Determination of whether intermediate haemoglobin concentrations (6–10 g dl^{-1}) justify or require RBC transfusion should be based on the patient's risk for complications of inadequate oxygenation.

(3) The use of a single haemoglobin "trigger" for all patients and other approaches that fail to consider all important physiological and surgical factors affecting oxygenation is not recommended.

(4) When appropriate, preoperative autologous blood donation, intraoperative and postoperative blood recovery, acute normovolaemic haemodilution, and measures to decrease blood loss (deliberate hypotension and pharmacological agents) may be beneficial.

(5) Indications for transfusion of autologous RBC may be more liberal than for allogeneic RBC because of the lower (but still significant) risks associated with the former.

However, the Task Force Report stated clearly that "controlled studies have not been performed to determine the haemoglobin concentration at which RBC transfusion improves clinical outcome", a point echoed in the accompanying editorial: "the efficacy of this biologic [red blood cells] has not been demonstrated in an appropriately controlled, prospective study".

The report and editorial also noted specific concerns of the anaesthetist: variations in anaesthetic agents and technique, depth of anaesthesia and intraoperative hypothermia may all influence the response to anaemia, and signs and symptoms of inadequate tissue oxygenation are absent or difficult to interpret under anaesthesia.[5] Furthermore, myocardial ischaemia is often silent and likely to occur in the less intensively monitored postoperative period. Faced with such uncertainties, one understands how the anaesthetist may be tempted to err on the side of transfusion. In a different journal, an editorial worried that "the pendulum has swung too far in the direction of avoidance of transfusion", arguing that the "anesthesiologist's challenge (and duty) is to prevent ischemia and infarction, not to wait until they occur and then treat them".[6] The unspoken assumption behind the statement is, of course, that blood transfusion actually prevents ischaemia and infarction, an assertion for which few data exist. In this article, we review the risks of anaemia and transfusion, and show how little evidence exists to support the efficacy of red cell transfusion. We also discuss some of our own recent findings on surgical anaemia and transfusion. We emphasize clinical data relevant to the anaesthetist and comment only briefly on animal or physiological studies.

Risks of anaemia

Data on the level(s) of anaemia at which risks for adverse events increase should be the basis for transfusion guidelines, but such data are limited.

ANIMAL DATA

Normal animals tolerate acute haemodilution to a haemoglobin concentration of 3–5 g dl^{-1}. As haemoglobin concentrations decrease to less than 5 g dl^{-1}, ischaemic electrocardiographic changes begin to appear, and as concentrations further decrease to less than 3 g dl^{-1}, lactate production, depressed ventricular function and death occur.[7-11] In theory, chronic anaemia should be better tolerated than acute anaemia because there is opportunity for intracellular

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2,3-diphosphoglycerate concentrations to increase and the oxyhaemoglobin dissociation curve to shift towards increased oxygen release, but whether or not this is true is unknown. In animal models, coronary artery disease increases susceptibility to anaemia. For example, even at relatively high haemoglobin concentrations of 7–10 g dl^{-1}, dogs with experimental coronary stenoses from 50% to 80% began to exhibit ST-segment changes or locally depressed cardiac function, or both.[8 11 12]

HUMAN DATA

There are few human data on the risks of anaemia. Thirty-five normal resting adults undergoing large volume haemodilution maintained adequate oxygen delivery to haemoglobin concentrations of 5 g dl^{-1}.[13] Obviously, these results may not be applicable to patients undergoing the stresses of surgery. Four older observational studies explored the effect of haemoglobin concentrations less than 10 g dl^{-1} in operative patients.[14–17] However, these studies were unable to control for confounding factors and evaluate risk at different haemoglobin concentrations. Viele and Weiskopf reviewed 61 reports from 1970 to early 1993 of Jehovah's Witnesses with haemoglobin concentrations <8.0 g dl^{-1} or packed cell volume <24% who declined blood transfusion for religious reasons.[18] All deaths attributed to anaemia occurred at haemoglobin concentrations ≤ 5 g dl^{-1}. The authors acknowledged the significant limitations of their approach but suggested that patients may tolerate even very low haemoglobin concentrations.

We recently published a cohort study of nearly 2000 Jehovah's Witness patients undergoing surgery.[19] In contrast with patients without cardiovascular disease, the risk of death in patients with cardiovascular disease began to increase sharply as preoperative haemoglobin concentrations decreased to less than 10 g dl^{-1} (fig. 1). We found a similar relationship between postoperative haemoglobin concentration and mortality. Lower pre- and postoperative haemoglobin concentrations were also associated with increased risks of morbidity. We also found that the effect of blood loss was greater in patients with a lower preoperative haemoglobin concentration. All of the above studies, including ours, describe only the natural history of anaemia and provide no information on whether or not transfusion modifies the risks of anaemia.

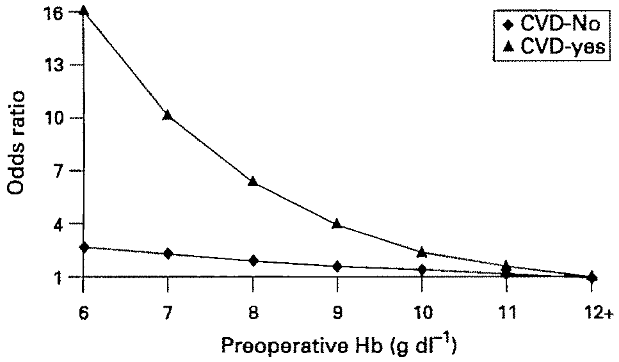

Figure 1 Relationship between preoperative haemoglobin (Hb) concentration and adjusted odds ratio for death, stratified by cardiovascular disease (CVD).

Risks of transfusion

POST-TRANSFUSION VIRAL HEPATITIS

The estimated risk of contracting hepatitis C has decreased markedly from approximately 5% per unit in 1985 to only 0.001% per unit in the latest data. Hepatitis B now represents the most common transfusion-borne viral infection (table 1).[20]

HIV

In the public's mind, HIV is the most dreaded risk of transfusion, yet modern testing has nearly eliminated HIV from the US blood supply.[21 22] The risk of transmission by transfusion is extremely low because there is only a 3-week time span during which the donor is infected but the test is not positive.[23–25] Based on the most recent estimates, the risk of HIV is 0.0002% per unit of blood.[22]

OTHER INFECTIONS

Other infections acquired through transfusions include cytomegalovirus, parasitic and bacterial infections. Except in severely immunocompromised patients, most cytomegalovirus infections are clinically insignificant. The incidence of transfusion-transmitted parasitic and bacterial infections is vanishing.[26]

NON-HAEMOLYTIC AND HAEMOLYTIC TRANSFUSION REACTIONS

Fever, chills and urticaria occur in 1–5% of red cell transfusions and generally do not cause major morbidity or mortality.[27] These symptoms may in fact be masked by general anaesthesia.

In contrast, haemolytic transfusion reactions from the erroneous administration of ABO incompatible blood can be disastrous. A recent estimate of the incidence of human error was approximately 1 in 24 000 transfusions, but data are limited.[28] Unfortunately, a significant proportion of fatal transfusion reactions occur during surgery, where the reaction may be more difficult to diagnose. Symptoms of a transfusion reaction may either be masked by general anaesthesia or may be non-specific (hypotension, tachycardia, disseminated intravascular coagulation) and attributed to other causes.[4]

IMMUNOSUPPRESSION

The most important risk of allogeneic blood transfusion may be an immunosuppressive effect leading to increased bacterial infections. Numerous observa-

Table 1 Residual risk of viral infections from allogeneic blood transfusion. *HTLV=T-cell lymphotropic virus type-1 and type-2 From Schrieber and colleagues.[19 20]

	Residual risk (infections per million donations)
HIV	2.03
HTLV*	1.56
Hepatitis C	9.7
Hepatitis B	15.83
Total	29.12

tional studies report an association between allogeneic transfusion and bacterial infections.[29–34] However, many of these studies did not adequately control for confounding risk factors for infections, such as the use of Foley catheters despite the high frequency of urinary tract infections in these studies. Randomized clinical studies avoid the problem of confounding but have, unfortunately, yielded conflicting results. Two studies compared allogeneic with autologous blood transfusion. One study found a lower infection rate in patients receiving autologous blood[35] while the other found no difference.[36] Three randomized studies compared leuco-depleted blood with packed red cells; two found a lower risk of infection with leuco-depleted blood[37 38] while the third found an equal infection risk.[39] Thus the risk of bacterial infection with allogeneic blood transfusion remains uncertain but urgently needs further study and clarification as postoperative infections are an important cause of mortality and morbidity in surgical patients.[40–42]

Efficacy of transfusion

OBSERVATIONAL STUDIES

While human data on adverse effects of anaemia are few, studies on clinical outcome of RBC transfusion are even less common and have found little impact from red cell transfusions.[43–46] Previous studies have examined physiological variables such as oxygen transport and metabolic responses rather than clinical end-points such as mortality, morbidity or functional status. Most of the studies were performed in critically ill medical patients, and not in surgical patients.[44–46]

A recent study in 4470 critically ill patients examined the impact of transfusion practice on mortality rates.[47] Patients who died in intensive care units had lower haemoglobin values and were transfused red cells more frequently. In patients with cardiac disease, increasing haemoglobin values in anaemic patients was associated with improved survival suggesting that blood transfusion itself improved survival.

Our group recently reported the largest study to date on the impact of perioperative transfusion. We studied 30- and 90-day postoperative mortality in 8787 consecutive hip fracture patients undergoing surgical repair.[48] Patients with haemoglobin concentrations of 8.0–10.0 g dl^{-1} had highly variable chances of receiving transfusions, but more than 90% of patients with haemoglobin concentrations less than 8 g dl^{-1} were transfused. In multivariate analyses that controlled for haemoglobin concentration, cardiovascular disease and other risk factors for death, we found no effect of postoperative transfusion on 30-day mortality (adjusted odds ratio=0.96, 95% confidence interval 0.74–1.26) or 90-day mortality (adjusted hazard ratio=1.08, 95% confidence interval 0.90–1.29) (table 2). Similarly, we found no effect for preoperative transfusion. Thus in this group of elderly surgical patients, perioperative transfusion at a haemoglobin concentration of 8 g dl^{-1} or higher appeared to have no impact on the risk of short- or long-term death. We could not draw any conclusions on the effects of transfusion in patients with haemoglobin concentrations less than 8 g dl^{-1} as nearly all patients with this degree of anaemia were transfused.

RANDOMIZED CLINICAL TRIALS

Only well performed, randomized, clinical studies can unambiguously define the efficacy of transfusion as observational studies may suffer from confounding (patients receiving transfusion are different from those not receiving transfusion in ways that may not be adequately controlled statistically).

We are aware of only five published randomized studies comparing different transfusion triggers in a total of 207 patients (table 3).[49–53] None of the studies found any differences in mortality or morbidity between high and low transfusion thresholds but the studies had inadequate power to detect clinically important outcomes.

Table 2 Effect of postoperative transfusion on 30-day mortality, stratified by trigger haemoglobin concentration. *Adjusted for multiple confounding variables. From Carson and colleagues[48]

Trigger haemoglobin stratum	*n*	Adjusted odds ratio for death* (95% confidence interval)
Overall	8787	0.96 (0.74–1.26)
$\geq$10 g dl^{-1}	3215	0.91 (0.45–1.82)
8.0–9.9 g dl^{-1}	4452	1.29 (0.94–1.76)
7.0–7.9 g dl^{-1}	906	1.01 (0.37–2.77)
Cardiovascular disease–yes	5004	1.19 (0.79–1.80)
Cardiovascular disease–no	3783	1.07 (0.75–1.52)

Table 3 Randomized clinical studies contrasting different thresholds for blood transfusion. GI bleed=gastrointestinal, CABG=coronary artery bypass grafting, ICU=intensive care unit

Author	Year	*n*	Setting	Protocol
Topley	1956	22	Trauma	11.3 *vs* 15.6
Blair	1986	50	GI bleed	2 units *vs* 0 units
Weisel	1992	27	CABG	7.0 *vs* 12.0
Johnson	1992	39	CABG	8.3 *vs* 10.7
Hebert	1995	69	ICU	7–9 *vs* 10–12
Carson	1998	84	Hip fracture	10 g dl^{-1} *vs* symptomatic transfusion

We have recently completed a pilot study to assist planning for a large clinical study in hip fracture patients.[54, 55] Patients were randomized during the first 3 days after surgery if postoperative haemoglobin concentration was <10 g dl^{-1}. The study contrasted the effect of symptomatic transfusion *vs* a 10-g dl^{-1} threshold. In the symptomatic transfusion group, transfusion was given for symptoms related to anaemia (e.g. chest pain that is possibly cardiac in origin). Transfusion was permitted but not mandatory if the haemoglobin concentration decreased to less than 8 g dl^{-1}. In the 10-g dl^{-1} threshold group, patients were given as much blood as necessary to maintain the haemoglobin concentration greater than 10 g dl^{-1}. This study will be the first to assess the widely recommended strategy of reserving transfusion only for symptomatic patients. Results from the pilot study showed substantially lower transfusion rates in the symptomatic group. The outcomes were very similar in the groups except for the 60-day mortality in which five (11.9%) patients in the symptomatic group and two (4.8%) in the 10-g dl^{-1} threshold group died (relative risk=2.5; 95% confidence interval 0.5–12.2; P=0.43). We estimate that approximately 12 000 patients must be randomized to have 90% power to detect a 20–25% difference between the two transfusion strategies on 30- and 60-day mortality, morbidity and functional status.

Conclusion

Unfortunately, data to guide transfusion decisions are scant. There has never been a randomized clinical study large enough to assess the effects of different transfusion thresholds on mortality, morbidity or functional status. Observational studies suggest that patients with underlying cardiovascular disease are more susceptible to anaemia, but our recent study, the largest to date, found no benefit from transfusion in patients with cardiovascular disease. As observational studies may be limited by bias and power, there is a compelling need for a large clinical study. A recent editorial summarized our current state of knowledge: "blood transfusions clearly are lifesaving for some patients and unnecessary for others, but, remarkably, for many patients the benefits of transfusion are not known....these results support the need for systematic study, such as a randomized clinical trial, of the benefits of perioperative blood transfusion for these patients".[56]

Given the current lack of evidence, the guidelines promulgated by the American Society of Anesthesiologists represent a reasonable approach to perioperative red blood cell transfusion. We recommend using a higher transfusion threshold in patients with cardiovascular disease. Until better data become available, anaesthetists must continue to rely on clinical judgement to guide transfusion decisions.

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Transfusion requirements in critical care (TRICC): a multicentre, randomized, controlled clinical study

P. C. HÉBERT FOR THE TRANSFUSION REQUIREMENTS IN CRITICAL CARE INVESTIGATORS AND THE CANADIAN CRITICAL CARE TRIALS GROUP

Anaemia is common in the critically ill and results in the frequent use of red cell transfusions.[1 2] For decades, an arbitrary transfusion threshold of 100 g litre^{-1} has been used widely in clinical medicine, including the management of critically ill patients.[3] Recently, a re-evaluation of this practice was prompted both by the fear of transfusion-related infections such as AIDS and the prospect of an ever decreasing blood supply.[4–6] These concerns also resulted in the formulation of red cell transfusion guidelines by several organizations.[7–10] However, published guidelines, for the most part, have not addressed how red cells should be administered in critically ill patients.

These patients are affected by complex metabolic, respiratory and cardiovascular changes which predispose them to the adverse consequences of anaemia, such as the potential risk of myocardial infarction and death. It is also possible that critically ill patients are at increased risk of adverse consequences from allogeneic red cell transfusions, particularly the immunosuppressive[11–16] and microcirculatory[17–19] effects of red cells.

Despite the conflicting rationale for different approaches to the administration of red cells, there are few, well controlled clinical studies evaluating transfusion practice (table 1). In a recent systematic review of transfusion practice,[20] five randomized controlled clinical trials (RCT) contrasted two transfusion strategies in the perioperative and critical care setting (table 2).[21–25] All studies were too small to provide clinically useful inferences in critically ill patients. Transfusion decisions in critically ill patients are based therefore on studies evaluating adaptive responses to anaemia[26] and transfusions, or observational studies and poorly controlled clinical trials.[20] To elucidate better the risks and benefits of transfusions, we conducted a large, randomized, controlled clinical study to determine if mortality rates, organ dysfunction and several secondary outcomes were similar following a restrictive or liberal transfusion strategy in normovolaemic, critically ill patients. In this article, the background outlining the divergent risks and benefits of a restrictive and a liberal approach to the transfusion of allogeneic red cells and the study design implemented in the Transfusion Requirements in Critical Care (TRICC) study are discussed.

Transfusion practice variation in critical care

As an initial step in the planning of a large RCT, the TRICC trial investigators agreed that significant practice variation was a necessary precondition for a large RCT contrasting two existing approaches to the administration of red cells. Two observational studies, a survey of critical care physicians and a large cohort study were conducted to determine individual and hospital practice variation.

In a 1993 Canadian survey of critical care practitioners,[27] we documented that 35% of respondents identified 90 g litre^{-1} as the minimum haemoglobin concentration and an additional 40% selected 100 g litre^{-1}. Baseline transfusion thresholds ranged from a low of 50 g litre^{-1} to 120 g litre^{-1}. Thresholds were significantly different ($P<0.001$) between conditions (fig. 1). All clinical characteristics evaluated, except congestive heart failure ($P>0.05$), significantly changed transfusion thresholds of Canadian critical care practitioners ($P<0.0001$). We also noted significant differences among the four case histories and several potential risk factors. There was a significant association between having an academic affiliation and transfusion practice ($P<0.0001$). Physicians with an academic affiliation transfused red cells at a lower threshold than non-academics. When grouped into four major geographic locations (West, Ontario, Quebec, East), with no more than five academic centres per region, we noted that there was a statistically significant difference ($P<0.01$) in baseline transfusion thresholds across all case histories. In a second study with a cohort of 4470 patients, we also documented a significant variation in nadir haemoglobin concentrations before transfusion among six academic intensive care units using multivariate techniques adjusting for the influence of diagnosis, disease severity, patient age and transfusion status ($P<0.0001$).[28] Both studies provide compelling evidence of significant individual, institutional and regional variation in critical care transfusion practice, indicating uncertainty regarding optimal haemoglobin concentrations and the need for further study.

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Table 1 Theoretical reasons supporting the restrictive or liberal use of allogeneic red cells in normovolaemic critically ill patients

Rationale supporting the liberal use of red cells
(1) Augmenting oxygen delivery may improve survival
(2) Increased risk of coronary ischaemia because of increased demand
(3) Age, disease severity and drugs may interfere with adaptation to anaemia
(4) Improved safety margin if further blood loss

Rationale supporting the restrictive use of red cells
(1) Red cell transfusions impair microcirculatory flow
(2) Pathological supply dependency is rare
(3) Risk of viral infection
(4) Immunodepression causing increased infections after transfusion
(5) Cardiac consequences of red cells less important

Evidence for restrictive and liberal approaches to transfusion

The liberal use of red cells in critically ill patients may be justified on the basis that oxygen delivery should be increased or maintained at high values in critically ill patients because of the possibility of continuing tissue damage from ischaemia. Sepsis and the adult respiratory distress syndrome (ARDS)[29–47] may induce tissue hypoxia by producing an abnormally increased anaerobic threshold. Below this threshold or critical value of oxygen delivery, oxygen consumption decreases as oxygen delivery decreases. This abnormal linear relationship is often referred to as "pathological supply dependence". The resultant tissue hypoxia may eventually contribute to the evolution of irreversible multiple system organ failure followed by death. Indeed, two prospective observational studies[35 39] found a significant association between mortality and the occurrence of pathological supply dependence.

Several clinical studies[48–50] have attempted to define optimal levels of oxygen delivery in critically ill and high-risk perioperative patients. All seven randomized, open-labelled, clinical studies[48–54] evaluated therapeutic interventions other than red cells to augment oxygen delivery. A recent meta-analysis combining results from these studies suggested greater benefit in the perioperative period from augmented oxygen delivery.[55] However, there is still little consensus as to which patients are most likely to benefit from increased oxygen delivery and which intervention is superior (i.e. fluids, red cells, inotropic agents or some combination of these). It is also important to note that all published RCT maintained haemoglobin values greater than 100 g litre^{-1}, hence inferences regarding optimal red cell transfusion strategies were not possible.

In addition to RCT, we identified 14 before and after studies (table 3) evaluating the impact of red cell transfusions on oxygen kinetics. Oxygen delivery uniformly increased but oxygen consumption was observed to change in only five of the studies. The lack of change in oxygen consumption reflects either methodological errors,[56] or patients who did not have an increased anaerobic threshold, rather than an indication that red cells were unnecessary, as suggested by one of the studies.[57] In summary, liberal administration of allogeneic red cells using a threshold of at least 100 g litre^{-1} may be justified based on the presence of pathological supply dependency in critically ill patients.[3 58 59]

Critical care practitioners may opt to transfuse more liberally in patients considered at risk of coronary artery disease or having established cardiac disease. Two large cohort studies have documented that increasing degrees of anaemia were associated with a disproportionate increase in mortality rates in the subgroup of patients with cardiac disease. Critically ill patients[1] with cardiac disease had a trend towards increased mortality when haemoglobin values were <95 g litre^{-1} (55% *vs* 42%; P=0.09) compared with anaemic patients with other diagnoses. Patients with anaemia, a high APACHE II score (>20) and a cardiac diagnosis had a significantly lower mortality rate when given 1–3 or 4–6 units of allogeneic red cells (55% (no transfusions) *vs* 35% (1–3 units) or 32% (4–6 units), respectively; P=0.01). In Jehovah's Witness patients undergoing surgery,[60] the adjusted odds of death increased from 2.3 (95% confidence interval (CI) 1.4–4.0) to 12. 3 (95%CI 2.5–62.1) as preoperative haemoglobin values declined from 100–109 g litre^{-1} to 60–69 g litre^{-1} in patients with cardiac disease. In non-cardiac patients with comparable levels of anaemia, there was no effect of anaemia on mortality. Even though both studies were observational in nature and may not have controlled for several important confounding variables, it appears that anaemia increases the risk of death in patients with cardiac disease. As a corollary, moderate levels of anaemia may be tolerated safely in critically ill patients with other diagnoses.

A more conservative approach to the administration of red cells in the perioperative setting has been advocated by many clinical practice guidelines.[7 9] Most of these guidelines highlight the risks associated with transmission of viruses such as HIV and hepatitis through transfusions as an important concern. In addition to direct transmission of viruses, critically ill patients may also be at increased risk of adverse consequences from allogeneic red cell trans-

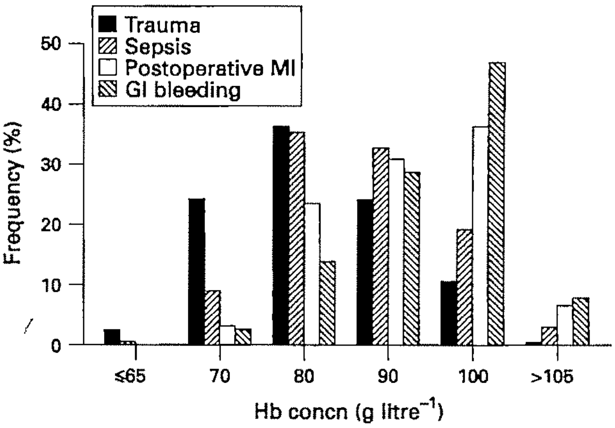

Figure 1 Baseline transfusion thresholds for the four clinical situations in the national survey of critical care practitioners The range of haemoglobin (Hb) concentrations below which red cells would be administered, for each of the four situations (trauma, sepsis, postoperative myocardial infarction (MI) and gastrointestinal (GI) bleeding) is illustrated. The distributions of the thresholds were significantly different between situations (P<0.001, Kruskal–Wallis test statistic). Respondents were more reluctant to administer red cells to the trauma patient than to a stable elderly patient with a gastrointestinal haemorrhage. Physicians did not respond uniformly in their decisions regarding infusion of red cells to the development of congestive heart failure.

Table 2 Randomized clinical trials of transfusion practices in perioperative and critically ill patients. Hb=Haemoglobin concentration; CABG=coronary artery bypass grafting; GI=gastrointestinal; PCV=packed cell volume

Author/year published	Level of evidence	No. of patients	Study population	Intervention	Outcome	Comments
Weisel[21] (1984)	II	27	CABG	Crystalloid alone (n=14) *vs* blood or colloid solutions (n=13)	[Hb] lower in crystalloid group 20 h post-operation (P=0.01) Reduction in blood use in the crystalloid group No difference in pulmonary oedema and haemodynamic variables (cardiac index and filling pressures)	Small sample size No difference in mortality or myocardial infarction rates Delayed recovery of myocardial extraction in a small number of patients in the crystalloid group
Johnson[22] (1992)	II	38	CABG	Conservative group PCV maintained at 25% (n=20) *vs* liberal group PCV maintained at 32% (n=18)	Conservative group transfused with fewer units than the liberal group (P= 0.012) Mean cardiac index same for both groups in the OR and 1 day postop. Mean postop. LOS:7.6±1.9 days (liberal), 7.9±4.3 days (conservative) No difference in fluid requirement, haemodynamic variables or hospital complications No relation between exercise tolerance on the 5th and 6th days and PCV	Small sample size No postoperative deaths reported No difference in ischaemic event
Blair[25] (1986)	II	50	GI haemorrhage	At least 2 units of PRC (immediate) (n=24) *vs* no transfusion unless [Hb] < 80 g litre^{-1} (delayed) (n=26)	Decrease transfusions in delayed group (2.6 *vs* 4.6 units/patient, P<0.05) The number of re-bled patients was greater in the immediate transfusion group (9 *vs* 1, P<0.01)	Small sample size Study design included a pilot study Laboratory and clinical measurements available No detailed data related to operative interventions and mortality rate Prolonged clotting time and higher re-bleeding rate due to blood transfusions in the first 24 h
Fortune[23] (1987)	II	25	Adult trauma	PCV=30% (n=12) *vs* PCV=40% (n=13)	5 units of PRC more in PCV=40% groups No difference in haemodynamic variables Higher intrapulmonary shunt in PCV=40% group	Small sample size Physiologic outcome measurements only No data on mechanisms and type of traumatic injury No data on clinical outcomes
Hébert[24] (1995)	II	69	ICU	Restrictive group: [Hb]=70–90 g litre^{-1} (n=33) *vs* liberal group: [Hb] =100–120 g litre^{-1} (n=36)	Average daily [Hb]=90 g litre^{-1} *vs* 109 g litre^{-1} (P< 0.001) Number of units transfused 48% less in restrictive group (2.5 *vs* 4.8 units/patient) No difference in mortality and organ failures (P>0.05) No difference in ICU and hospital LOS (P>0.05)	Small sample size Pilot unable to detect difference in clinically important outcomes

fusions, particularly the immunosuppressive and microcirculatory effects of red cells. In a search of the literature, we identified six randomized, controlled, clinical studies examining the role of transfused red cells in immune modulation.[11–16] There were mixed results from these studies. Only three studies, comparing either leuco-depleted red cells[13,14] or autologous transfusions[16] with allogeneic transfusions, demonstrated decreased rates of postoperative infection. If allogeneic red cells result in clinically important immune suppression, this may cause significant increases in the rates of nosocomial infection, multisystem organ dysfunction and death, given that infection is a major cause of morbidity and mortality in the ICU.

While the effects of haemoglobin concentration (packed cell volume) on systemic oxygen transport in the central circulation have been well studied, it remains unclear how increasing packed cell volume values may affect oxygen delivery in the microcirculation.[61–63] There are many storage-related changes in red cells[5,64–73] and changes caused by diseases such as sepsis[17–19,74,75] that decrease red cell deformability and the ability to off-load oxygen in the microcirculation. In conjunction with significant systemic microcirculatory dysfunction observed in many critically ill patients, the decrease in red cell deformability may affect markedly tissue oxygen delivery in many critically ill patients.[17–19,74] Thus there is evidence to suggest that red cell transfusions increase systemic oxygen delivery but may have adverse effects on microcirculatory oxygen delivery to the tissues.

As described above, we identified only five RCT attempting to contrast all of these benefits, risks, harms and costs of red cell transfusion in a total of 209 patients. One of the studies enrolled otherwise healthy patients with gastrointestinal haemorrhage. The study documented an increase in coagulation abnormalities after the use of a more liberal transfusion strategy. Patients undergoing coronary revascularization were included in two studies.[21,22] In a study by Johnson and colleagues,[22] 39 patients were allocated randomly to receive either a liberal transfusion strategy (maintaining a packed cell volume of 32% or haemoglobin concentration of 105 g litre^{-1}) or a conservative approach (maintaining a packed cell volume of 25% or haemoglobin concentration of 82 g litre^{-1}). There were no differences in postoperative complication rates in the two groups even though the conservative group experienced a significant decrease in total postoperative blood use. A second RCT, carried out by Weisel and colleagues,[21] assessed day 5 exercise tolerance and haemodynamic and myocardial metabolic response after normovolaemic haemodilution in 27 patients. Patients received red cells if haemoglobin concentration decreased to less than 120 g litre^{-1} in addition to colloids (n=13) *vs* crystalloids and allogeneic red cells only if haemoglobin concentration decreased to less than 70 g litre^{-1} (n=14). Although patients in the low haemoglobin group received significantly less red cell transfusions, there were no differences in morbidity, mortality or exercise tolerance. In a small subset of patients (n=6), there were differences in the rate of myocardial lactate recovery in the low haemoglobin group, suggesting increased myocardial ischaemia from anaemia. Hébert and colleagues[24] allocated randomly 69 critically ill patients to a restrictive red cell transfusion strategy (haemoglobin concentration of 70–90 g litre^{-1}) or a liberal strategy (haemoglobin concentration of 100–120 g litre^{-1}) to evaluate the effect of the treatments on mortality rate, organ dysfunction score and other markers of morbidity. The results showed that neither mortality nor development of organ dysfunction was affected by the transfusion strategy. However, maintenance haemoglobin concentrations of 70–90 g litre^{-1} decreased the mean number of units transfused from 4.8 to 2.5 units (48% reduction; P<0.001). Finally, a clinical study in critically ill trauma victims allocated randomly 25 patients to allogeneic red cell transfusions when packed cell volume reached either 30% or 40%. The authors concluded that there were no discernable differences in oxygen transport variables between the transfusion strategies.[23] In summary, all five studies enrolled too few patients to make significant inferences regarding important outcomes from red cell transfusions.

From this review, it is apparent that an optimal and safe lower limit of the transfusion threshold has not been established in critically ill patients.[76] Therefore, there is a need for further randomized, controlled, clinical studies.

Overview of the TRICC trial

INTRODUCTION

The Transfusion Requirements in Critical Care (TRICC) study is a randomized, clinical trial designed to answer the question of whether conservative and liberal transfusion strategies are similar in usual clinical ICU practice. We believe that a clinical study should demonstrate that both strategies are equally safe and effective (equivalent). If the treatments are found to be equivalent, then a lower threshold may be recommended in critically ill patients. In addition, analysis of subgroups using secondary outcomes planned in this study will permit a detailed evaluation of the intervention where clinically relevant.

In the planning phase of this study, we chose to implement a study design that reflected a compromise between the "efficacy" and "effectiveness" approaches (table 4). Study characteristics are frequently quite dissimilar. Efficacy studies generally opt for restricted eligibility, rigorous treatment procedures and disease-specific outcomes responsive to the potential benefits of the experimental intervention. A similar study attempting to determine effectiveness would implement liberal eligibility criteria, loosely defined treatment procedures and outcomes which represent overall response to an intervention.

STUDY POPULATION

In this study, we enrolled patients admitted to one of 22 tertiary concentration intensive care units (ICU) and three community ICU in Canada, between November 1, 1994 and November 14, 1997. All ICU had a full time intensivist or a critical care team caring for patients on a daily basis. We included patients who: (1) were expected to stay more than 24 h; (2) had a haemoglobin concentration ≤90 g litre^{-1} within

Table 3 Thirteen studies examining oxygen delivery, oxygen consumption and lactate before and after red cell transfusion. ↑Do_2=increased oxygen delivery; ↑$\dot{V}o_2$=increased oxygen consumption; NA=not available. *Authors only indicated average haemoglobin change not number of units transfused

Author/year published	Study population	No of patients	Average No. transfusions	Changes in measurements of post-transfusion ↑Hb	↑Do_2	↑$\dot{V}o_2$	↓Lactate	Comments
Ronco[31] (1990)	PCP pneumonia	5	1.5 u	Yes	Yes	Yes	NA	All patients had ↑lactate at baseline. Thermodilution used for $Do_2/\dot{V}o_2$ measurements.
Fenwick[32] (1990)	ARDS	24	1.5 u.	Yes	Yes	No	No	Normal lactate (n=1) compared with high lactate (n=13) group.
				Yes	Yes	No	Yes	Used haemodilution catheter for all measurements. Significant increases in Vo_2 in response to transfusion in high lactate group
Ronco[29] (1991)	ARDS	17	1.5 u.	Yes	Yes	No	NA	Normal lactate (n=7) compared with high lactate group (n=10). No relationship between Vo_2 and Do_2 when Vo_2 directly measured with expired gases.
Shah[82] (1982)	Post-trauma	8	1 or 2 u.	Yes	Yes	Yes	NA	1 RBC unit (n=5) or 2 units (n=3) given to patients. Thermodilution used for Do_2/Vo_2 measurements.
Steffes [83] (1991)	Postoperative + post-trauma	21	1-2 u.	Yes	Yes	Yes	No	27 measurements sets in 21 patients. Thermodilution used for Do_2 and Vo_2 measurements. Increased lactate values did not predict Vo_2 response.
Babineau[57] (1992)	Postoperative	31	328±9 ml	Yes	Yes	No	NA	32 of 33 transfusions were single units. Thermodilution used for Do_2/Vo_2 measurements. 58% of transfusions did not increase $\dot{V}o_2$.
Gilbert[33] (1986)	Septic	17	Δ 20 g litre^{-1}*	Yes	Yes	No	No	33 measurement sets in 31 patients. 10 of 17 patients had increased lactate. Vo_2 significantly increased in high group only.
Dietrich[84] (1990)	Medical shock (septic/cardiac)	32	577 ml	Yes	Yes	No	No	36 measurement sets in 32 patients. No change in Vo_2 after transfusion. Thermodilution used for $Do_2/\dot{V}o_2$ measurements.
Conrad[30] (1990)	Septic shock	19	Δ30 g litre^{-1}*	Yes	Yes	No	No	Normal lactate (n=8) compared with high lactate (n=11) group No increase in Vo_2 with transfusion in either group. Thermodilution used for Do_2/Vo_2 measurements.
Marik[85] (1993)	Septic	23	3 u.	Yes	Yes	No	No	Do_2 measured independently of $\dot{V}o_2$. Using gastric tonometry, patients receiving old red cells developed evidence of gastric ischaemia.
Lorente[86] (1993)	Septic	16	2 u.	Yes	Yes	No	NA	Dobutamine significantly increased $\dot{V}o_2$ while red cells did not. Thermodilution used for Do_2/Vo_2 measurements.
Mink[87] (1990)	Septic shock 2 mo–6 yr	8	8–10 ml kg^{-1} × 1–2 h	Yes	Yes	No	NA	In paediatric patients, $\dot{V}o_2$ did not increase with red cells. Thermodilution used for Do_2, $\dot{V}o_2$ measurements.
Lucking[88] (1990)	Septic shock 4 mo–15 yr	7	10–15 ml kg^{-1} × 1–3 h	Yes	Yes	Yes	NA	8 measurement sets in 7 patients Thermodilution used for Do_2/Vo_2 measurements.

Table 4 Comparison of study characteristics using either an efficacy or effectiveness approach when designing a study. *Data monitoring refers to the review of source documents and adjudication/verification of outcomes

Study characteristics	Efficacy study (explanatory trials)	Effectiveness study (pragmatic trials)
Research question	Does the intervention work under ideal conditions?	Will the intervention result in more good than harm under usual practice conditions?
Setting	Restricted to centres of excellence	Open to all institutions
Patient selection	Specific diseases in well-defined patients	Wide range of patients identified using broad eligibility criteria
Study design	Small single or multicentre study	Very large multicentre clinical trial
Baseline assessment	Elaborate and detailed	Simple and clinician friendly
Intervention	Tightly controlled Optimal therapy under optimal study conditions	Less controlled Therapy administered According to usual care
Treatment protocols	Rigorous and detailed Compliance essential	Very general Non compliance tolerated
Endpoints	Disease-related Related to biological effect "Surrogate" end-points (e.g. allogeneic exposure)	Patient-related (e.g. all-cause mortality or quality of life)
Analysis	By treatment received Non-compliers excluded	Intention-to-treat All patients included
Data management		
Data collection	Elaborate	Minimal and simple
Data monitoring*	Detailed and rigorous	Minimal

72 h of ICU admission; and (3) were considered volume resuscitated or normovolaemic by the attending staff. Patients were excluded for any of the following reasons: (1) less than 16 yr of age; (2) enrolment in another interventional study; (3) unable to receive blood products; (4) active blood loss at the time of enrolment, defined as a decrease in haemoglobin of 30 g litre^{-1} in the preceding 12 h or requiring at least 3 units of packed red cells during the same period; (5) chronic anaemia defined as at least one haemoglobin concentration ≤90 g litre^{-1} documented more than 1 month before hospital admission; (6) pregnancy ascertained by history, physical examination or confirmed using βHCG; (7) brain dead or not expected to survive more than 24 h; (7) moribund and not expected to survive more than 24 h; (9) expected duration of stay in the ICU less than 24 h; (10) lack of commitment from attending staff to continue active treatment of the patient; and (11) admitted after routine cardiac surgical interventions. The study was approved by the Research Ethics Board of each participating institution. Informed consent was obtained from the patient or the closest family member.

At baseline, we obtained patient characteristics, diagnostic information, medication use and information necessary to complete the acute physiological and chronic health evaluation score.[77] We also noted the number of organs failing and the multiple organ dysfunction (MOD) score at baseline, in addition to several variables related to oxygen delivery, including use of vasoactive drugs, fluid administration, Pa_{CO_2} values and arterial saturation, and cardiac output where available. In addition, haemoglobin concentration and the number of units transfused before randomization were noted. In terms of assigning a diagnosis and diagnostic category, we chose to report the diagnosis most responsible for the patient's admission to the ICU. In postoperative patients, we noted the procedure performed and the responsible diagnosis. The cardiovascular category included all diagnoses related to ischaemic heart disease (myocardial infarction, angina, congestive heart failure and cardiogenic shock), rhythm disturbances, cardiac arrest, and cardiac and vascular surgical procedures, including abdominal aortic aneurysm and peripheral vascular surgical procedures. The multiple trauma category included both blunt (≈90%) and penetrating injuries. The respiratory category included pneumonia, chronic obstructive pulmonary disease, asthma, respiratory arrest, acute respiratory distress syndrome (non-cardiogenic pulmonary oedema) and respiratory failure from other causes. All data were obtained from the clinical record by research nurses and coded using the ICD-9 classification system by an expert data analyst. The accuracy of diagnoses was verified by the principal investigator.

STUDY DESIGN AND TREATMENT PROCEDURES

We undertook a prospective, multicentre, randomized, controlled equivalency study to compare two transfusion strategies in normovolaemic critically ill patients. Patients were allocated randomly to one of two treatment groups by consecutive allocation from a random listing stratified by centre and disease severity using APACHE II scores[77] (APACHE II scores <15 or ≥15) and blocked by balanced groupings of 10.[78] Sealed sequential opaque envelopes were distributed to each participating ICU. All envelopes were returned to the coordinating centre and audited periodically.

Transfusion guidelines for both the restrictive and liberal treatments were developed through a consensus building process involving the TRICC Trial Executive Committee, the Canadian Critical Care Trials Group and faculty of the University of Ottawa, Clinical Epidemiology Unit in addition to information from the national survey of Canadian critical care practitioners[27] and a pilot version of this study.[24] The following principles were used in developing the two transfusion ranges: (1) safety of each specific range; (2) current transfusion practice in Canadian ICU; and (3) general acceptability of each specific range. When randomized, a patient's haemoglobin concentration was maintained using allogeneic red cell transfusions, as required. In patients allocated to the restrictive strategy, haemoglobin concentrations were maintained at 70–90 g litre^{-1} with a transfusion trigger of 70 g litre^{-1}. In patients allocated to a liberal transfusion strategy, haemoglobin concentrations were maintained at 100–120 g litre^{-1} with a transfusion trigger of 100 g litre^{-1}. Blinding of treatment allocation was not feasible.

In addition to the study interventions, physicians in both groups were also advised to transfuse red cells, 1 unit at a time, and to measure haemoglobin concentrations after each unit. The study interventions were required only during the stay in the ICU. On discharge from the study, a copy of the American College of Physicians' (ACP) guidelines[7] was placed in the patient's medical record. Compliance with the transfusion procedure was monitored by examination of haemoglobin concentration and transfusion records sent to the study coordinating centre on a monthly basis. Individual centres were given regular feedback as to their ability to maintain haemoglobin concentrations in the target range.

OUTCOME MEASURES

The primary outcome measure in this study was the 30-day all-cause mortality. Secondary outcomes included other mortality rates, such as ICU mortality, hospital mortality and survival times. We also examined different measures of organ failure and dysfunction, including the number of organ failures,[39,79] rates of multiple system organ failure (MSOF), as defined by Hébert and colleagues,[79] and multiple organ dysfunction score (MODS), as defined by Marshall.[80] Patients who died were assigned an MSOF score of 7 and a MOD score of 24 as a means of incorporating mortality into the scores.

Complications were also recorded. These included: (1) cardiac events, defined as episodes of unstable angina, myocardial infarction or cardiac arrest; (2) pulmonary events, defined as adult respiratory distress syndrome and nosocomial pneumonia; (3) haematological events, defined as transfusion reactions, haemolytic reactions and disseminated intravascular coagulation; (4) gastrointestinal events, defined as gastrointestinal haemorrhage, bowel perforation and ischaemic bowel; (5) infections, defined as bacteraemia and cannula sepsis; and (6) neurological complication, defined as cerebral vascular accidents and encephalopathy. As part of the complications, we also recorded requirements for surgical interventions, dialysis and mechanical ventilation. Finally, duration of ICU and hospital stay was recorded.

Conclusions

Around the world, issues related to blood safety from transmission of viruses have resulted in devastating health consequences and major changes to the delivery of blood in many countries. This same fear continues to fuel a multi-billion dollar industry aiming to develop new technologies to replace red cells (e.g. oxygen carrier) or minimize patient exposure (e.g. drugs such erythropoietin and aprotinin, techniques such as haemodilution and perioperative autologous transfusion). In the perioperative setting, drugs such as erythropoietin and aprotinin decrease allogeneic exposure by one to two red cell units on average,[81] often costing several thousands of dollars without any evidence of overall effectiveness. In contrast, the TRICC trial pilot study[24] demonstrated that maintaining haemoglobin concentrations between 70 and 90 g litre^{-1} decreased the mean number of units transfused from 4.8 to 2.5 units (48% reduction; $P<0.001$). In the present study, we hope to demonstrate that such a simple and cheap intervention is not only efficacious in decreasing allogeneic red cell use but is also safe and perhaps superior in high-risk patients.

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Haemoglobin therapy in clinical practice: use and characteristics of DCLHb

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Allogeneic blood transfusions are the only medical option for treating major blood loss. Currently, an estimated 13 million units of whole blood are donated each year in the USA,[1] 17 million units in Europe and another 6 million units in Japan.[2] However, shortages in blood supply still occur and can pose a serious risk, particularly in patients suffering from severe trauma and shock. In addition, shortages can result in delays in elective surgery procedures.

STORAGE AND DEGRADATION

Heightened public awareness may serve to prevent seasonal blood shortages. However, blood must be refrigerated and can be stored for no more than 6 weeks.[3] It is possible to freeze donated blood in glycerol, but this process is slow and the thawed red cells are rapidly labile. Therefore, blood banks are unable to stockpile blood to prepare for disaster scenarios.

In addition, blood stored for more than 2 weeks exhibits impaired oxygen transport. This is caused by loss of red cell 2,3-diphosphoglycerate (2,3-DPG), which is responsible for maintaining the low affinity conformation of the haemoglobin tetramer. As 2,3-DPG stores are not replenished *in vivo* until several hours after transfusion, oxygen delivery to tissues is reduced when it is most required. Longer storage of blood is also associated with increased haemolysis, decreased pH and increased plasma potassium concentrations.[3]

PRE-HOSPITAL EMERGENCIES

Donated blood requires typing and cross-matching, serving to delay the transfusion of blood and prevent the immediate resuscitation of patients after a trauma event. Type O-negative blood is a scarce resource, and although it is generally available in hospital emergency departments, it is rarely transported on ambulances, even for the most severe trauma emergencies. In such circumstances the current pre-hospital resuscitation techniques involve infusion of large volumes of crystalloid or colloid solutions, or both. However, a recent study has questioned the use of large volumes of such crystalloids, which may actually increase bleeding, impair clotting, decrease tissue oxygen delivery and increase mortality.[4] Various oncotically active colloids, which are less likely to affect coagulation, may be used more widely in Europe.

DISEASE TRANSMISSION RISK

Significant improvements in the safety of the human blood supply have been achieved in recent years by technical developments, more thorough donor screening and public education programmes. Despite these improvements, an as yet unidentified or less well characterized blood-borne disease might possibly endanger transfusion recipients. Furthermore, management of potential risks to the blood supply has led to questions of cost effectiveness as ever more sensitive and expensive tests have been used and much needed blood products have been recalled.

In response to these potential risks, the use of preoperative autologous blood donations has become increasingly popular. Surgeons may use expensive drugs and perioperative blood cell salvage techniques to avoid allogeneic transfusions. Furthermore, surgical techniques to minimize blood loss have been developed and surgeons will allow their patients to develop a greater degree of postoperative anaemia. However, the risks of under transfusion in patients have not yet been fully quantified.[5]

IMMUNOMODULATION

Allogeneic blood transfusion down-regulates cellular immunity, which may lead to decreased natural killer cell function, macrophage migration and lymphocyte proliferation.[6] Immune suppression and transfusion reactions, although often minor, still occur in approximately 10% of transfused patients.[7]

Haemoglobin solutions as alternatives to blood

Oxygen-carrying alternatives to blood have been clinically tested since Amberson and colleagues administered haemoglobin–saline solutions in clinical studies in the 1940s.[8 9] In one of these early studies, 14 patients received an injection of a haemoglobin–saline solution. Of these, five patients with secondary anaemia caused by haemorrhage or infection received multiple injections and three of these patients showed clinical improvement, consisting of increased haemoglobin and packed cell volume values and reticulocytosis.[9] However, the use of these

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early haemoglobin solutions had several drawbacks, including renal impairment, resulting from short intravascular persistence and impurities of the haemoglobin introduced during preparation.[9–11]

The first generation of haemoglobin solutions has addressed the infectious disease risk, storage, stability and typing issues described earlier and are now in clinical trials. These solutions can improve the oxygen-carrying capacity of patients' red blood cells and help avoid allogeneic transfusion. Their potential may be in clinical emergencies where typed and cross-matched blood is not available. These solutions may also be useful in treating disease arising from inadequate blood flow and ischaemia, such as stroke, heart attack and sickle cell anaemia.

Sources of haemoglobin

Early oxygen carriers involved the use of "stroma-free" haemoglobin solutions.[11] These solutions did not require blood typing or cross-matching and could be stored for long periods. However, removal of haemoglobin from red cells leads to loss of 2,3-DPG and diminished oxygen–delivery characteristics. Furthermore, haemoglobin tetramers tend to dissociate into dimers, which have a short intravascular persistence (because of rapid renal excretion) and a nephrotoxic action secondary to dimer precipitation in the proximal tubule.[10] Recently, methods have been developed to prevent these problems by chemically modifying and stabilizing the haemoglobin molecule. Several haemoglobin therapeutics are now in clinical studies as temporary alternatives to blood or as therapeutic agents for ischaemia. The various haemoglobin products under development are derived from three principal sources: human, bovine and genetically engineered haemoglobin.

HUMAN HAEMOGLOBIN

The rationale for using human haemoglobin is related to the reduced risk of allergic or other immune reactions in the recipient. The viral risks associated with blood transfusions, already reduced by extensive donation screening tests, are greatly minimized during manufacture by rigorous viral inactivation procedures. Some chemically stabilized haemoglobin solutions, such as diaspirin crosslinked haemoglobin (DCLHb; HemAssist, Baxter Healthcare Corporation) are subjected to ultrafiltration and heat treatment during the manufacturing process to inactivate viruses.[12–14] Several human haemoglobin-based products are advancing through clinical studies, including DCLHb, which is currently in phase III clinical trials in Europe and the USA.

Other human haemoglobin-based products are currently being developed, including pyridoxylated and glutaraldehyde polymerized haemoglobin (PolyHeme, Northfield Laboratories Inc.), O-Raffinose crosslinked and polymerized haemoglobin (HemoLink, Hemosol Inc.) and pyridoxylate haemoglobin polyoxyethylene (PHP) (Apex Corporation).

BOVINE HAEMOGLOBIN

Bovine haemoglobin is readily available and may be less costly than human haemoglobin.[15] In common with human haemoglobin, bovine haemoglobin requires modification to be clinically effective. Infectious agents present in animal blood, such as the bovine spongiform encephalopathy (BSE) prion, are not as well characterized and therefore are more difficult to detect than those in human blood. Products from animals must also be subjected to rigorous purification procedures, as contamination with animal-derived proteins may cause allergic reactions in humans. Bovine haemoglobin is usually derived from protected herds in countries without BSE. In addition, the specific purification techniques used may be able to eliminate the protein responsible for BSE transmission even though the nature of the protein is unknown.

A bovine haemoglobin product was approved recently for veterinary use in dogs (Oxyglobin, Biopure Corp.). A second bovine haemoglobin, glutaraldehyde polymerized bovine haemoglobin (Hemopure, Biopure Corp.), is in phase III human clinical studies in Europe, and a third bovine-derived product, polyethylene-glycol conjugated bovine haemoglobin (Enzon), is in phase I trials.

GENETIC ENGINEERING

Recombinant technology is also being investigated to engineer oxygen carrying solutions. These techniques allow flexibility in product design, enabling haemoglobin molecules to be modified to address specific clinical needs. In addition, many of the potential side effects of bovine-sourced products, or the sourcing complications associated with human red blood cells, may be avoided by using recombinant technology. Purification requirements for recombinant products are high, but the source material is theoretically unlimited. The only recombinant haemoglobin product to enter clinical studies to date is a modified human haemoglobin tetramer crosslinked with a glycine bridge between the alpha subunits (Optro, Somatogen Inc.).

Haemoglobin solutions in clinical practice: a profile of DCLHb

DCLHb is produced using 3,5-dibromosalicylate to form a four-carbon fumarate bridge between the two alpha subunits of the haemoglobin molecule. Stabilization of DCLHb during manufacture not only permits heat treatment but also induces the haemoglobin to assume a low-affinity conformation similar to that in the human red blood cell in the presence of 2,3-DPG. Consequently, DCLHb has similar oxygen carrying properties to fresh blood. However, DCLHb has a slightly higher P_{50} than fresh blood (right-shifted oxygen dissociation curve), which allows it to release oxygen more readily to tissues compared with red blood cells.

DCLHb, administered at doses of approximately 20–1000 ml, has been investigated in several clinical studies in patients undergoing orthopaedic, abdominal aortic repair and major abdominal surgery; patients in haemorrhagic, hypovolaemic shock; critically ill patients with septic shock failing conventional therapy; and those suffering from acute anaemia or acute ischaemic stroke. In completed studies involving more than 700 patients, safety assessments indicated that DCLHb was well tolerated.[16–19]

In a small study, DCLHb (750 ml) effectively eliminated the need for transfusion of blood for a period of 7 days in one-third (four of 12) of patients undergoing elective hip arthroplasty with high blood loss. A larger study in cardiac surgery patients after bypass who needed transfusion was undertaken to determine the efficacy of DCLHb in reducing or preventing postoperative use of blood transfusions.[17] In this multicentre study, 209 patients were enrolled if they required transfusion after bypass. Patients were allocated randomly to receive up to three doses (total 750 ml) of DCLHb or up to three units of packed red blood cells (pRBC) within 24 h after bypass. DCLHb reduced transfusion of pRBC in 59% of recipients on the day of surgery, when all patients in the control group received allogeneic blood. On the day after surgery, 39% of patients who received DCLHb had still not received blood. At 7 days after surgery, 19% of the DCLHb-treated patients had completely avoided transfusion of pRBC. The most common adverse reactions were transient and non-serious and consisted of hypertension, yellowing of the skin (reported as jaundice), haemoglobinuria and hyperamylasaemia. There were no clinical sequelae from these events.

A recent study in critically ill patients indicated that DCLHb is an active vasopressor which, combined with its oxygen-carrying effects, may have future clinical applications, particularly in the prevention of ischaemia and reduction of organ failure and mortality in critically ill patients.[19] Further studies with DCLHb in other patient populations and using different dosing regimens are underway.

Future developments

The properties of haemoglobin solutions include effective transport and delivery of oxygen, similar to red cells. However, unlike the red cell, the haemoglobin molecule in solution may pass more easily into capillaries because of its small molecular size and low solution viscosity. These properties, and vasopressor effects, suggest other possible uses.

In an emergency, haemoglobin solutions may permit emergency department personnel to avoid time-consuming and expensive cross-matching, and allow more effective resuscitation of trauma patients.[18] Furthermore, haemoglobin solutions can be formulated to exert a colloid osmotic pressure which, combined with vasopressor activity, can increase arterial pressure without effects on regional perfusion. As a result, haemoglobin solutions may treat hypotension while maintaining regional perfusion in patients with septic shock. Other potential indications for haemoglobin solutions include stroke and myocardial infarction,[20,21] perfusion of tumours to enhance cancer therapy[22,23] and sickle cell anaemia.[24]

Haemoglobin solutions under investigation are relatively short-lived compared with transfused red cells, which limits future applications. Other solutions that may have a longer persistence and may be closer to the concept of "blood substitutes" are being developed. These include liposome-encapsulated haemoglobin, synthetic haem-embedded lipid microspheres and other oxygen-carrying "artificial red cells". Research efforts to create type O red cells by enzymatically altering type B or A red cells may prove successful in the future. Additionally, coating the red cell with polyethylene glycol may accomplish a similar purpose, but the other issues inherent in allogeneic transfusion remain in either case. Cloning of antigen-free, virus-free blood cells in tissue culture remains a theoretical possibility.

Conclusion

Preclinical studies have shown haemoglobin solutions to be as effective as blood and more effective than standard colloid or crystalloid solutions for resuscitation from haemorrhagic and septic shock. In early clinical studies, these solutions have been well tolerated, with only minor side effects. Haemoglobin solutions could provide an important new option for the treatment and prevention of ischaemia resulting from hypoperfusion. They could provide immediate on-site replacement for traumatic blood loss, prevent global ischaemia and organ failure, treat focal ischaemia and provide effective haemodynamic support for septic shock-induced hypotension. Results of further efficacy studies will reveal if the promise of these solutions will be fulfilled.

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Influence of haemoglobin concentration after extracorporeal circulation on mortality and morbidity in patients undergoing cardiac surgery

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The primary physiological role of haemoglobin is to transport oxygen from the lungs to the cells. A severe decrease in haemoglobin concentration (Hb) impairs oxygen delivery and the aim of red blood cell (RBC) transfusion is to improve inadequate oxygen delivery. Unfortunately, transfusion of RBC is not without risks and therefore unnecessary transfusions must be avoided. The haemoglobin concentration at which transfusion is required (i.e. the "transfusion trigger") remains largely undetermined for several reasons. First, it is often difficult to distinguish between true anaemia (decreased haemoglobin mass) and haemodilution. Second, the adverse effects of anaemia are compounded by factors such as age and the presence and severity of other illnesses that impair compensation for decreased oxygen content of blood. Finally, the beneficial effects of transfusion have not been demonstrated convincingly.

The argument for perioperative RBC transfusion assumes that: (a) adverse outcomes result from diminished oxygen-carrying capacity and (b) RBC transfusions, by enhancing oxygen-carrying capacity, can prevent these adverse outcomes.[1]

Tolerance limits to acute normovolaemic anaemia have not been established, but oxygen delivery is thought to remain adequate in most individuals at haemoglobin concentrations as low as 70 g litre^{-1}.[2] In healthy, normovolaemic individuals, tissue oxygenation is maintained and anaemia is tolerated at packed cell volume values as low as 18–25%; the heart does not begin producing lactic acid until a packed cell volume of 15–20% is reached, and heart failure usually does not occur until packed cell volume reaches 10%.[1] Profound intraoperative normovolaemic haemodilution to mean haemoglobin concentrations of 30 g litre^{-1} is clinically acceptable in children undergoing scoliosis surgery.[3] Similarly, conscious healthy resting adults tolerate acute isovolaemic reduction of haemoglobin concentration to 50 g litre^{-1} without evidence of inadequate oxygen transport.[4]

The two principal mechanisms responsible for maintaining normal oxygen delivery in the event of decreasing haemoglobin concentrations are increased cardiac output and increased oxygen extraction at the site of delivery. When the ability to compensate for anaemia has been exceeded, tissue dysoxia occurs, with reduction of non-essential functions,[5] and then irreversible organ damage, depending on the severity and duration of oxygen deprivation. It has been suggested that the need for RBC transfusion may be estimated by measuring whole-body oxygen consumption, oxygen extraction ratio and oxygen delivery, but such an estimate of RBC requirements has not been validated and, more importantly, is not organ specific. Whole-body oxygen consumption may be adequate in the presence of inadequate oxygen delivery to specific organs or to regions within these organs.[6]

It is generally accepted that the margin of safety for tolerance of low haemoglobin concentration is decreased by cardiovascular disease but, until recently, few data were available to substantiate this belief. A small case control study of 27 high-risk patients undergoing infra-inguinal arterial bypass procedures showed that myocardial ischaemia and morbid cardiac events were associated with a packed cell volume <28%, suggesting that postoperative anaemia may play a role in cardiac morbidity in this high-risk patient population.[7] A recent retrospective cohort study of 1958 surgical patients who declined blood transfusion for religious reasons found that, overall, the risk of mortality increased as the haemoglobin concentration decreased, but cardiac surgery patients were excluded from the study.[8]

Patients with severe cardiovascular disease or who have undergone high-risk cardiovascular procedures do not tolerate anaemia as well as other critically ill patients.[9] In such patients, transfusion of 1–6 units of RBC was associated with a 40% decrease in mortality compared with patients who did not receive any transfusion. In a retrospective study of 2738 sequential patients undergoing myocardial revascularization, Fang and colleagues showed that minimum packed cell volume during extracorporeal circulation was an independent risk factor for mortality after coronary artery surgery.[10] Overall, mortality increased with packed cell volume values ≤14% and, in high-risk patients, with values ≤17%.

Immediately after cardiac surgery, oxygen demand is increased, myocardial function is often compromised and the heart may be unable to compensate for anaemia. Haemoglobin concentrations as low as those described by Fang and colleagues may not be

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tolerated in the immediate postoperative period. Furthermore, haemoglobin concentration may influence not only mortality, but also morbidity. This effect may differ according to the type and complexity of the surgical procedure (revascularization, valve surgery, reoperations, combined procedures, etc.). Thus, we sought to determine the influence of nadir haemoglobin concentration during the first 24 h (haemoglobin concentration minimum (min) 24 h) after extracorporeal circulation on mortality and morbidity in patients undergoing a variety of cardiac surgical procedures.

Patients and methods

This retrospective study included all patients (*n*=2661) undergoing myocardial revascularization or valvular surgery, or both, from January 1995 to December 1996 at the Montreal Heart Institute, a tertiary care institution dedicated to the care of cardiac patients. During this time, our routine clinical practice was an opioid-based anaesthetic, supplemented with volatile agents as required, extracorporeal circulation (ECC) with a membrane oxygenator, arterial line filter and roller pump, with very moderate hypothermia (32–34°C) and sanguineous cardioplegia. After surgery, patients were transferred to the intensive care unit and, 24–48 h later, to the ward according to clinical progress. Rapid extubation is performed whenever possible. During cardiopulmonary bypass, haemoglobin concentrations as low as 60 g litre^{-1} are tolerated if venous oxygen saturation and blood lactate concentrations remain acceptable. After extracorporeal circulation, haemoglobin concentrations as low as 80 g litre^{-1} are tolerated if the patient is haemodynamically stable. However, it is not uncommon for patients to present with lower haemoglobin concentrations at some time during the immediate postoperative period because of blood loss from the mediastinal drains.

The department of anaesthesia maintains a comprehensive database that includes all patients undergoing cardiac surgery. Approximately 150 variables are collected on every consecutive patient in three separate sections: preoperative, intraoperative and postoperative data. The preoperative section comprises patient characteristics, and cardiovascular, co-morbidity, medication and laboratory data. The intraoperative section is designed to collect information on the surgical procedure, cardiopulmonary bypass, use of vasopressors and fluid balance. Estimated blood loss and use of blood products are also documented. The postoperative section is completed after hospital discharge and includes mortality, morbidity and duration of stay in the intensive care unit and hospital. Data on postoperative chest drainage, blood loss, nadir haemoglobin concentration and packed cell volume within the first 24 h after surgery and use of blood products are collected. Preoperative and intraoperative data are collected from the anaesthesia form while postoperative data are collected by a dedicated research assistant. All data are verified by one of the investigators (R. M.) both before and after entry into our computerized database.

The end-points of the study were postoperative mortality (death occurring during the postoperative period, before hospital discharge), morbidity and duration of hospital stay. Morbidity comprises seven complications, each of which is defined according to the criteria presented in table 1. Duration of hospital stay (in days, from the day of surgery until discharge) was included as an indicator of morbidity, as it reflects the quality of postoperative progress and the overall clinical significance of the complications collected. Thus a total of nine outcome variables were studied. The 25 variables listed in table 2 were selected as potential risk factors for postoperative mortality and morbidity. Five factors were analysed as continuous variables (age, body mass, duration of ECC, preoperative haemoglobin concentration and preoperative creatinine concentration), while the other 20 were treated as dichotomous variables.

Finally, while not a primary objective of this study, the influence of postoperative erythrocyte transfusion, administered presumably to correct a low haemoglobin concentration, was examined.

Table 1 Definition of morbid events after extracorporeal circulation

Complication	Definition	Frequency
Haemodynamic	Vasopressors/inotropes >24 h Intra-aortic balloon pump counterpulsation Cardiac arrest (resuscitated)	*n*=343
Myocardial infarction	CK-MB >100 or more in the first 3 postoperative days or documentation of MI in the chart	*n*=210
Pulmonary	Tracheal intubation ≥48 h or reintubation necessitated by respiratory condition	*n*=126
Infectious	Sepsis Pulmonary, wound or catheter site infection	*n*=113
Neurological	Coma, convulsions Neurological deficit (transient or permanent)	*n*=134
Renal	Increase of serum creatinine 100 μmol litre^{-1} or more within 1 week	*n*=134
Abdominal	Increase in liver enzymes three times upper limit of normal Gastrointestinal bleeding Paralytic ileus associated with mesenteric ischaemia Postoperative laparotomy	*n*=138

Table 2 Preoperative risk factors used in the prediction of postoperative morbidity and mortality

Variable	Definition	Category
Age		Continuous
Sex		0 = male 1 = female
Body mass		Continuous
Diabetes	Diabetes requiring medication	0 = No; 1 =Yes
Heparin	Preoperative use of heparin	0 = No; 1 =Yes
Aspirin	Preoperative use of aspirin	0 = No; 1 =Yes
LV dysfunction	Severe preoperative left ventricular dysfunction	0 = No; 1 =Yes
CHF	Congestive heart failure	0 = No; 1 =Yes
Angina	Preoperative unstable angina	0 = No; 1 =Yes
Recent MI	Myocardial infarction in the past 6 weeks	0 = No; 1 =Yes
IABP	Preoperative intra-aortic balloon pump counterpulsation	0 = No; 1 =Yes
COPD	Chronic lung disease	0 = No; 1 =Yes
Tobacco	Active use of tobacco	0 = No; 1 =Yes
Creatinine	Creatinine concentration (μmol litre^{-1})	Continuous
Hypertension	History of hypertension	0 = No; 1 =Yes
CVD	Cerebrovascular disease	0 = No; 1 =Yes
Surgery	Type of operation performed	1= Revascularization 2 =Valve
Priority	Degree of surgical emergency	0 = Urgent + stat 1 = Elective
Redo	Reoperative procedure	0 = No; 1 =Yes
[Hb] preop	Preoperative haemoglobin concentration	Continuous
NVH	Intraoperative normovolaemic haemodilution	0 = No; 1 =Yes
Transfusion	Intraoperative transfusion of red cells	0 = No; 1 =Yes
EACA	Intraoperative E-aminocaproic acid	0 = No; 1 =Yes
Aprotinin	Intraoperative aprotinin	0 = No; 1 =Yes
ECC time	Duration of extracorporeal circulation	Continuous

STATISTICAL ANALYSIS

Univariate analyses were performed to determine potential risk factors associated with the nine end-points examined (eight dichotomous and one continuous). When appropriate, the Pearson's chi-square test, Student's *t* test and one-way ANOVA with Satterthwaite's and Welch's correction, respectively, in the case of a lack of homogeneity or univariate linear regression were used to assess the significance of the 25 predictors selected. These univariate results (appendix 1) must be examined with caution because of the possible relationships between the variables studied.

All risk factors with a *P* value less than 0.15 were entered in a backward stepwise multiple logistic regression for each of the dichotomous outcomes, and backward multiple linear regression for the continuous outcome. The variables age, sex, body mass, diabetes, preoperative haemoglobin concentration, duration of ECC and haemoglobin concentration min 24 h were included in all models, irrespective of their association with the outcome measures. Potential pairwise interactions with haemoglobin concentration min 24 h were also included in the backward procedure. The exclusion significance level was set at 0.05. The fit of the final logistic regression model was assessed by the Hosmer–Lemeshow statistic chi-square$_{HL}$.[11] All tests were two-sided. Analyses were performed using the SAS/STAT software, release 6.12 (SAS Institute, Inc., Cary, NC, USA).

Results

Myocardial revascularization included primary (n=1828) and repeat (n=152) operations. Valvular surgery included patients undergoing aortic valve replacement (n=207), mitral valve repair or replacement (n=152), multiple valve surgery (n=131), and valve surgery associated with myocardial revascularization (n=191). Valvular surgery was reoperative in 28.2% of cases. Sixteen patients died during operation and were excluded. The general characteristics of the population studied are presented in table 3. Overall, mortality rate was 2.9% and patients stayed in hospital for an average of 8 days during the study. The frequency of postoperative complications is presented in table 1.

Detailed results of the univariate analysis are presented in appendix 1. Preoperative congestive heart failure, type of operation performed, reoperative procedure, intraoperative transfusion of red cells, use of aprotinin and duration of ECC were strongly associated with all nine outcome variables. Minimal postoperative haemoglobin concentration had a statistically significant association with all postoperative complications except myocardial infarction, pulmonary complications and death, although the *P* value for the latter was 0.06. However, haemoglobin concentration min 24 h was not a significant predictor of postoperative death by multivariate analysis.

Nadir postoperative haemoglobin concentration was significantly associated with duration of hospital stay by multiple linear regression analysis, and with renal and abdominal complications by multiple logistic regression analysis. Predictors selected by the statistical procedure are presented in table 4. Parameter estimates (β), odds ratios and confidence intervals where applicable for each of these three outcomes are detailed in appendices 2–5. Non-significant values of the Hosmer–Lemeshow statistic suggested that the models fitted the observed outcomes well. These mathematical models showed that

Table 3 General characteristics of the patient population analysed (mean (SD) [range] or percent)

n=2661	
Age (yr)	63 [21–88]
Percent male (%)	70.2
Weight (kg)	74(15) [33–139]
Congestive heart failure (%)	28.1
Chronic renal failure (%)	6.9
Hypertension (%)	44.1
Myocardial revascularization (%)	74.4
Valvular surgery (%)	25.6
Elective *vs* urgent operation (%)	53/47
Preoperative [Hb] (g litre^{-1})	136(17) [75–197]
Minimal [Hb] 24 h post ECC (g litre^{-1})	81(12) [39–140]
Intraoperative transfusion of red cells (%)	27.8
Patients receiving aprotinin (%)	11.9
Patients receiving EACA (%)	32.1
Patients transfused allogeneic blood products (%)	68.62
Number of units transfused (in patients transfused)	9(17) [1–340]
Duration of extracorporeal circulation (min)	84(37) [14–521]
Duration of hospital stay (days)	8.3(6.7) [2–131]
Percent mortality (n=78) (%)	2.9

Table 4 Predictors of duration of hospital stay, and abdominal and renal complications by multivariate analyses

	Length of stay	Abdominal	Renal
[Hb] min 24 h	X	X	X
Sex	X		X
Age	X	X	X
Body mass	X		
LV dysfunction	X		
CHF	X	X	X
Hypertension			X
CVD		X	
Creatinine		X	X
[Hb] preop			X
Surgery	X		
Redo	X		
ECC time	X	X	X
EACA		X	X
Aprotinin	X	X	
[Hb] min 24 h–ECC time interaction	X		
[Hb] min 24 h–CHF interaction	X		
[Hb] min 24 h–Redo interaction	X		
[Hb] min 24 h–age interaction			X

duration of hospital stay and risk of developing renal or abdominal complications increased when the minimal postoperative haemoglobin concentration decreased.

In the case of renal complications, interaction of minimal postoperative haemoglobin concentration with age must be considered. The odds ratios calculated for renal complications taking into account the interaction with age are presented in appendix 5. The effect of haemoglobin concentration min 24 h on the odds of having renal complications decreased with increasing age, becoming statistically non-significant in patients aged 65 yr or older.

For example, in a typical 55-yr-old female patient with congestive heart failure undergoing reoperative valve surgery, decreasing the minimal postoperative haemoglobin concentration from 100 to 60 g litre^{-1} increased duration of stay from 10 to 17 days, the risk of abdominal complications from 7% to 13% and that of renal complications from 5% to 11%. Similarly, decreasing the minimal postoperative haemoglobin concentration from 100 to 60 g litre^{-1} increased duration of stay from 8 to 9 days, the risk of abdominal complications from 7% to 13% and that of renal complications from 8% to 10% in a typical 70-yr-old male with cerebrovascular disease undergoing primary myocardial revascularization.

Discharge haemoglobin concentration, number of erythrocyte transfusions administered, duration of stay and incidence of renal and abdominal complications are presented as a function of haemoglobin concentration min 24 h in table 5. Discharge haemoglobin concentration for the entire population was 102±12 g litre^{-1} (range 61–147 g litre^{-1}) and was the same, regardless of haemoglobin concentration min 24 h. In an attempt to differentiate the effects of postoperative anaemia from those of postoperative transfusions, duration of stay and incidence of renal and abdominal complications were ascertained according to the number of units of red blood cells transfused after operation, stratified for nadir haemoglobin concentration. Table 6 shows that both incidence of complications and duration of stay increased significantly with increasing erythrocyte transfusion, irrespective of haemoglobin concentration min 24 h.

Table 5 Erythrocyte transfusion, discharge [Hb] and complications for different concentrations of [Hb] min 24 h. *$P<0.05$ by one-way ANOVA with Dunnett's *post hoc* tests comparing [Hb] min 24 h <60 g litre^{-1} to the other [Hb] min 24 h concentrations, †$P<0.05$ by *post hoc* tests using log-linear models with Bonferroni's correction tests comparing [Hb] min 24 h <60 g litre^{-1} to the other [Hb] min 24 h concentrations

[Hb] min 24 h (g litre^{-1})	Postop RBC transfusion (units) (median [range])	Discharge [Hb] (g litre^{-1}) (median [range])	Length of stay (days) (mean (SD))	Renal complications (%)	Abdominal complications (%)
< 60	4[1–24]	96[76–127]	10.6(7.8)	11.48	11.48
60–69	3[0–26]	101[76–144]	9.6(9.2)	6.36	10.14
70–79	2[0–45]	99[70–147]	8.5(6.8)*	6.04	4.98
80–89	0[0–32]	100[71–145]	7.8(6.2)*	3.87†	4†
>89	0[0–11]	106[61–143]	7.6(4.9)*	3.54†	3.54†

Table 6 Duration of stay (days) and percentage of patients presenting an abdominal or renal complication according to [Hb] min 24 h and number of units of red blood cells transfused after operation (mean (SD))

		Postoperative RBC transfusions			
[Hb] min 24 h (g litre^{-1})	Extent	None	1-4 units	≥5 units	*P*
<60	Renal		0 1	20.7	0.046
	Abdominal		0.1	20.7	0.046
	Stay		9(6.7)	12.9 (8.6)	0.06
60–69	Renal	0	3.9	14.5	0.002
	Abdominal	0	0.3	28.9	0.001
	Stay	5.8(1.5)	8.6(7.7)	13.4(12.6)	0.005
70–79	Renal	3.5	5.2	15.4	0.001
	Abdominal	2.3	3 6	18.3	0.001
	Stay	6.9(2.9)	8.4(7.2)	12(7.9)	0.0002
80–89	Renal	1.7	5.0	27.6	0.001
	Abdominal	0.4	6.3	40	0.001
	Stay	6.9(3.6)	8.9(4.9)	17.2(28)	0.0001
>90	Renal	1.7	11.5	25	0 001
	Abdominal	1.1	13.8	37.5	0.001
	Stay	6.8(2.9)	11.2(7.4)	24(20)	0.0001

Discussion

In the past few years, it has been recommended that transfusion of allogeneic blood products (ABP) be avoided if possible for fear of transmission of viral disease and to conserve declining blood supplies. Several strategies were implemented in cardiac and major orthopaedic surgery where transfusion of ABP is frequent. Unfortunately, the risk/benefit ratios of several of these strategies, such as accepting very low postoperative haemoglobin concentrations, have not been examined critically. The risk/benefit ratio of erythrocyte transfusion has also not been studied. Therefore our results may be interpreted in two, opposing ways.

First, we can conclude that low haemoglobin concentrations in the immediate postoperative period increase postoperative complications significantly and that subsequent correction of anaemia by erythrocyte transfusion (table 5) did not modify the incidence of renal and abdominal complications. This suggests that transfusion was either insufficient, too tardy or incapable of correcting inadequate oxygen availability. The delay between diagnosis and treatment of anaemia, associated with susceptibility of renal and splanchnic beds to oxygen deprivation, could explain our findings. If this interpretation is correct, early prevention of a decrease in haemoglobin concentration would appear preferable to late treatment with transfusions, at least with respect to renal and abdominal complications.

In contrast, as the optimal transfusion threshold ("trigger") has never been determined in these patients, another interpretation of our results may be that the erythrocyte transfusions increased complications after surgery, rather than the anaemia per se. The fact that intraoperative transfusion was not an independent predictor by multivariable analysis militates against this hypothesis. Yet this interpretation is appealing when one considers that patients who were transfused with the highest nadir haemoglobin concentration were also those who presented the highest incidence of complications and stayed longest in hospital (table 6). It could be that these were sicker patients for whom the attending physician estimated that a greater haemoglobin concentration was required. If, in turn, this hypothesis is correct, this would indicate that transfusions were, at best, ineffective.

Thus the effects (either beneficial or deleterious) or the absence thereof of postoperative transfusion per se could not be determined in this study. Transfusions may be beneficial by correcting anaemia or coagulopathy in the perioperative period, or deleterious by their immunomodulatory and infectious effects. Further studies are needed to determine the relative contribution of transfusion to postoperative complications.

In acute anaemia, reductions in arterial oxygen content are usually well tolerated because of compensatory increases in cardiac output. Particularly in patients undergoing cardiac surgery, this compensatory mechanism may be affected by factors such as left ventricular dysfunction and pharmacological agents (anaesthetics, β-adrenergic or calcium channel blockers, etc.). Spahn and colleagues have shown that isovolaemic haemodilution to an average haemoglobin concentration of 99 g litre^{-1} was well tolerated and fully compensated in patients with coronary artery disease receiving β-adrenergic blockers chronically.[12] However, we do not know if patients with limited ability to increase cardiac output are able to tolerate lower haemoglobin concentrations during the perioperative period. Our study supports the observations of Carson and colleagues and Fang and colleagues mentioned previously.[8 10]

Postoperative complications result from complex interactions between patient risk factors and type of operation performed. Thus it is difficult to state a specific threshold for the risk of postoperative anaemia, as this risk varies considerably according to the clinical context and complication considered. Application of the statistical model to various clinical situations allows us to appreciate the variable importance of minimal postoperative haemoglobin concentration under different circumstances, although the models may not be adequate for extreme situations since such extremes occur infrequently and may not have been modelled adequately. Obviously, the association between haemoglobin concentration min 24 h and morbidity does not demonstrate a causal relationship. This association could be related to a covariable not included in the present study, such as the use of vasopressors, postoperative intra-aortic balloon counterpulsation, etc.

Several "non-medical" and organizational considerations may influence duration of stay. Nonetheless, its measurement is objective and, overall, clinicians recognize that duration of stay reflects the quality of postoperative progress. Similarly, renal dysfunction was defined by an objective criterion, comparable with that used by other authors.[13 14] As in the present study, Mangano and colleagues have shown that many patients undergoing elective myocardial revascularization develop postoperative renal dysfunction and failure, which are associated with prolonged hospital stay and greater need for specialized long-term care.[14] Thus prevention of postoperative renal complications and reduction of hospital stay should reduce the use of health care resources.

Contrary to our expectations, haemoglobin concentration min 24 h was not an independent predictor of postoperative myocardial infarction. In the perioperative period, cardiac function is monitored extensively and anomalies treated aggressively, possibly explaining this finding, in agreement with previous studies showing that very low haemoglobin concentrations can be tolerated after myocardial revascularization. Transfusions guided by clinical indications, while allowing packed cell volume to decrease to less than 25% resulted in similar exercise tolerance and no adverse clinical consequences compared with transfusions aimed at maintaining packed cell volume greater than 32% in patients undergoing myocardial revascularization.[15] Haemodilution to a packed cell volume of approximately 15% was well tolerated in anaesthetized humans after coronary artery bypass surgery, with no electrophysiological or metabolic evidence of myocardial ischaemia.[16] Haemoglobin concentration did not affect myocardial lactate flux in patients undergoing coronary artery bypass surgery, suggesting haemoglobin concentrations as low as 60–70 g litre^{-1} are well tolerated by the heart in the perioperative period.[17]

The interaction of age and perioperative anaemia on the risk of postoperative complications is not entirely clear, possibly because clinicians tend to avoid low haemoglobin concentrations in the elderly. At haemoglobin concentrations less than 80 g litre^{-1}, 90.5% of patients were transfused in a series of 8787 hip fracture patients aged 60 yr or older, preventing analysis of the association of transfusion with mortality.[18] Spahn and colleagues have shown that isovolaemic haemodilution to a mean haemoglobin concentration of 88 g litre^{-1} is well tolerated in elderly patients free from known cardiac disease aged 65–88 yr (mean 76 yr).[19] A previously healthy 84-yr-old male Jehovah's Witness maintained a normal oxygen consumption–delivery relationship at a haemoglobin concentration of 40 g litre^{-1} during massive bleeding from gastric surgery in a case described by van Woerkens, Trouwborst and van Lanschot.[20] Conventional teaching dictates that elderly patients are monitored closely and treated early in the face of declining haemoglobin concentrations but, again, this approach has not been validated.

In summary, minimum haemoglobin concentration during the first 24 h after extracorporeal circulation is associated with morbidity in patients undergoing a variety of cardiac surgical procedures. Progressive anaemia in the immediate postoperative period increases duration of hospital stay and the incidence of renal and abdominal complications. In this retrospective analysis of 2661 patients, it was not possible to differentiate the effects of anaemia from those of subsequent erythrocyte transfusion. Further prospective studies are needed to study the relative risks of transfusion and blood conservation strategies.

Appendix

Detailed statistical results.

Appendix 1 P values for the univariate association between predictors and outcome variables. *P>0.15

	Death	Haemodynamic	Myocardial infarction	Pulmonary	Infectious	Neurological	Renal	Abdominal	Duration of stay
Age	0.0001	0.0001	0.3766*	0.0521	0.0166	0.0033	0.0002	0.0016	0.0001
Sex	0.0001	0.0001	0.9713*	0.0328	0.9203*	0.0001	0.5992*	0.0212	0.0001
Body mass	0.0001	0.0001	0.0271	0.2957*	0.1613*	0.0001	0.0535	0.0001	0.0098
Diabetes	0.6036*	0.1579*	0.0904	0.2166*	0.4551*	0.9562*	0.0832	0.0802	0.6696*
Heparin	0.0049	0.0049	0.1205	0.1157	0.7353*	0.8609*	0.0012	0.0948	0.5371*
Aspirin	0.2995*	0.1205	0.0005	0.0445	0.0997	0.6540*	0.3979*	0.0662	0.4757*
LV dysfunction	0.3765*	0.1466	0.2935*	0.6891*	0.0422	0.0934	0.1558*	0.9636*	0.0198
CHF	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Angina	0.5969*	0.9119*	0.0394	0.4740*	0.0663	0.0129	0.6491*	0.0613	0.0001
Recent MI	0.1037	0.0058	0.3229*	0.6966*	0 7057*	0.3771*	0.5652*	0.9430*	0.0416
IABP	0.0032	0.0001	0.0001	0.0002	0.0674	0.9845*	0.7061*	0.2194*	0.0128
COPD	0.0004	0.0005	0.1641*	0.0004	0.0049	0.5950*	0.0038	0.0001	0.0001
Tobacco	0.2264*	0.0787	0.6478*	0.7938*	0.8476*	0.0439	0.0194	0.6944*	0.0001
Creatinine	0.0001	0.0001	0.6048*	0.0001	0.0001	0.0039	0.0001	0.0001	0.0005
Hypertension	0.1719*	0.5685*	0.3959*	0.3287*	0.3252*	0.0813	0.0017	0.2892*	0.0738
CVD	0.0219	0.0093	0.0861	0.0067	0.0015	0.0122	0.0051	0.0026	0.0114
Surgery	0.0001	0.0001	0.0001	0.0004	0.0009	0.0001	0.0025	0.0001	0.0001
Priority	0.2879*	0.4567*	0.0076	0.4269*	0.2955*	0.6746*	0.0179	0.0719	0.1046
Redo	0.0001	0.0001	0.0001	0.0001	0.0021	0.0001	0.0310	0.0001	0.0001
[Hb] preop	0.0001	0.0001	0.6776*	0.0001	0.0098	0.0001	0.0001	0.0001	0.0001
NVH	0.0178	0.0044	0.8470*	0.0963	0.1986*	0.0222	0.0028	0.0143	0.0043
Transfusion	0.0001	0.0001	0.0001	0.0001	0.0007	0.0001	0.0013	0.0001	0.0001
EACA	0.4721*	0.3652*	0.1058	0.0635	0.5795*	0.8560*	0.0004	0.0307	0.3217*
Aprotinin	0.0001	0.0001	0.0002	0.0005	0.0001	0 0071	0.1283	0 0001	0.0001
ECC time	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
[Hb] min 24 h	0.0601	0.0002	0.9943*	0.5326*	0.0358	0.0118	0.0008	0.0007	0.0001

Appendix 2 Predictors of duration of hospital stay by multiple linear regression analysis (r^2=0.1346)

Duration of hospital stay	Variable estimate (β)	Standard error of β	P value
Intercept	−10.289	2.621	0.0001
[Hb] min 24 h	0.055	0.029	0.0596
Sex	0.852	0.313	0.0066
Aprotinin	1.066	0.422	0.0117
Age	0.096	0.012	0.0001
Body mass	0.037	0.010	0.0003
ECC time	0.094	0.028	0.0007
LV dysfunction	0.565	0.256	0.0276
CHF	5.388	2.033	0.0081
Redo	8.630	2.743	0.0017
Surgery	1.837	0.362	0.0001
[Hb] min 24 h–ECC time interaction	−0.001	0.000	0.0134
[Hb] min 24 h–CHF interaction	−0.057	0.025	0.0224
[Hb] min 24 h–Redo interaction	−0.078	0.034	0.0210

Appendix 3 Predictors of abdominal complications by multiple logistic regression analysis (goodness-of-fit statistic: 6.528 with df=8; P=0.5883)

Abdominal complications	Variable estimate (β)	Standard error of β	P value	Unit	Odds ratio	Confidence interval	
						Lower	Upper
Intercept	−4.916	0.936	0.0001				
[Hb] min 24 h	−0.017	0.008	0.0351	10 (g litre^{-1})	0.843	0.718	0.987
EACA	0.458	0.206	0.0258	1.0	1.581	1.055	2.366
Aprotinin	0.559	0.260	0.0318	1.0	1.748	1.038	2.885
Age	0.022	0.009	0.0156	5 yr	1.119	1.023	1.227
ECC time	0.011	0.002	0.0001	15 min	1.179	1.111	1.253
CHF	0.550	0.197	0.0052	1.0	1.734	1.176	2.550
Creatinine	0 003	0.001	0.0031	25 μmol litre^{-1}	1.088	1.024	1.149
CVD	0.596	0.280	0.0334	1.0	1.816	1.019	3.074

Appendix 4 Predictors of renal complications by multiple logistic regression analysis (goodness-of-fit statistic: 6.539 with df=8; P=0.5870)

Renal complications	Variable estimate (β)	Standard error of β	*P* value
Intercept	8.643	4.108	0.0354
[Hb] min 24 h	−0.159	0.054	0.0032
Sex	−0.843	0.227	0.0002
EACA	0.683	0.191	0.0003
Age	−0.145	0.062	0.0182
ECC time	0.007	0.002	0.0015
[Hb] preop	−0.020	0.006	0.0011
CHF	0.706	0.206	0.0006
Creatinine	0.005	0.001	0.0001
Hypertension	0.549	0.192	0.0044
[Hb] min 24 h–age interaction	0.002	0.000	0.0071

Appendix 5 Renal complications: estimated odds ratio (OR) and 95% confidence intervals (CI) for each 10 g litre^{-1} increase in [Hb] min 24 h controlling for age[11]

	Age				
	50	55	60	65	70
OR	0.61	0.68	0.76	0.85	0.94
Lower CI	0.49	0.54	0.60	0.66	0.73
Upper CI	0.76	0.86	0.96	1.09	1.22

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Does optimizing oxygen transport improve outcome in intensive care patients?

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Although restoring normal haemodynamic values has always been assumed to be a therapeutic target for critically ill patients, recent studies reported increased values in oxygen transport variables in survivors of high-risk surgery.[1] The higher values observed in survivors may indicate physiological compensation for the increased metabolic requirements caused by the disease. The logical consequence has been to increase circulatory performance to values of cardiac index (CI) greater than 4.5 litre min^{-1} m^{-2} and oxygen delivery (Do_2) greater than 600 ml min^{-1} m^{-2}, which were threshold values that distinguished survivors from non-survivors.[2] This hypothesis was tested in different groups of patients,[3] producing contradictory results, although each seemed explicable. As treatment to obtain supranormal haemodynamic values often involves high doses of catecholamines which may be potentially dangerous, leading to arrythmia, myocardial ischaemia and infarction, assessment of this treatment in routine practice is clinically important.

We discuss the rationale and current evidence for the use of supranormal haemodynamic targets in the treatment of critically ill patients.

The rationale

Normal oxygen requirements of the body to maintain cellular integrity and normal function ($\dot{V}o_2$) is in the range 100–120 ml min^{-1} m^{-2} for a typical 70-kg adult. As the normal oxygen content of arterial blood (Ca_{O_2}) is 20 ml dl^{-1} and normal cardiac output is 5 litre min^{-1} for a typical adult, oxygen delivery (Do_2) exceeds that required to maintain $\dot{V}o_2$ which is normally largely independent of Do_2. If Do_2 decreases for any reason, $\dot{V}o_2$ remains stable over a wide range of Do_2 values while oxygen extraction (i.e. the ratio of arteriovenous oxygen difference to arterial oxygen content) increases. When Do_2 decreases below a critical value, $\dot{V}o_2$ decreases after oxygen extraction reaches its maximal level, and then $\dot{V}o_2$ becomes supply-dependent.[4] At this critical Do_2 value, identified as 300 ml min^{-1} m^{-2} in humans and 7–8 ml kg^{-1} min^{-1} in animals,[5] an increasing part of the energy requirement is met by anaerobic metabolism, creating a "hidden oxygen debt" which can be detected by observing an increase in $\dot{V}o_2$ when Do_2 is increased (oxygen supply dependency).

After a study by Powers and colleagues[6] in 1973, several authors studied the relationship between Do_2 and $\dot{V}o_2$ in patients with different forms of cardiovascular disease, such as adult respiratory distress syndrome (ARDS),[6 7] chronic obstructive lung disease,[8] sepsis syndrome,[9] pulmonary vascular disease[10] and congestive heart failure.[11] Although there are major differences between these studies, a common observation is that changes in Do_2 appear to be related to changes in $\dot{V}o_2$ for Do_2 values that are higher than its critical value (300 ml min^{-1} m^{-2}), suggesting that the mechanisms normally controlling tissue oxygen extraction could be impaired in disease states (pathological oxygen supply dependency).

The rationale for increasing oxygen delivery in critically ill patients is therefore based on the following hypotheses: (1) global or regional impairment of oxygen delivery to the cell creates an oxygen debt; (2) oxygen debt may induce anaerobic metabolism or impaired cellular function, or both; (3) oxygen debt may be detected by an increase in $\dot{V}o_2$ when Do_2 is increased; and (4) increasing Do_2 may, possibly, improve outcome.

The oxygen supply dependency

Several studies have reported on the relationship between Do_2 and $\dot{V}o_2$ in normal subjects or in patients: among the 80 recently evaluated by our group,[3] including a total of 4201 patients, the great majority were performed in sepsis (26 studies, 555 patients), ARDS (15 studies, 479 patients) and surgery (17 studies, 2262 patients). Four studies involved patients with mixed pathology (195 patients) while three studies were of groups such as cancer patients, obese patients with obstructive sleep apnoea and patients with hepatic failure. More than 70% (57 studies, 3537 patients) of these studies found an oxygen supply dependency, at least in some of the patients. The reverse Fick method was used to measure $\dot{V}o_2$ in 57 studies (3537 patients) and $Do_2/\dot{V}o_2$ dependency was found in 49 studies (3377 patients). In studies that used direct measurement of expired gases, 16 studies (3067 patients) were performed and only eight studies (50%) found similar results. Considering the 29 studies which evaluated

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the effect of increasing Do_2 on mortality, 24 (83%) reported improved outcome with increased Do_2, and $Do_2/\dot{V}o_2$ dependency was present in the great majority (21 studies, 88%). Lactic acidosis does not seem to influence the presence of oxygen supply dependency, shown by the fact that in 26 studies which reported lactate concentrations, a similar frequency of $Do_2/\dot{V}o_2$ dependency was observed in the presence (12 of 15 studies, 80%) or absence (eight of 11 studies, 73%) of lactic acidosis.

The results of this brief review deserve comment. First, the oxygen supply dependency is generally interpreted as the presence of a masked oxygen debt, which is paid when Do_2 is increased: this interpretation can easily be accepted in the presence of acidosis (unmasked oxygen debt), where oxygen debt is associated with anaerobic metabolism, but it appears more questionable in the absence of acidosis. An oxygen debt without anaerobic metabolism implies that, in the presence of impaired Do_2, the cell decreases, at least in part, its metabolic functions. This "starving-like state" would result in cellular organ dysfunction without immediate risk of death. Such a mechanism has never been investigated in detail, to our knowledge.

The second factor is the method used to study oxygen supply dependency. Most of the studies used the reverse Fick method to measure $\dot{V}o_2$ instead of direct measurement of expired gases. Concern about the validity of this convenient bedside method to determine if $\dot{V}o_2$ is dependent on Do_2 arises from artefactual bias, because there are variables common to both dependent ($\dot{V}o_2$) and independent (Do_2) terms of the relationship, and mathematical coupling of measurement errors shared in the common variables. This suggests a dependent relationship when, in truth, no dependency exists. Stratton, Feustel and Newell proposed a mathematical correction for the effect of mathematical coupling,[12] and converted data from previous studies of the $Do_2/\dot{V}o_2$ relationship in patients who had adult respiratory distress syndrome (ARDS).[13,14] They found that mathematical coupling did not significantly affect the positive slope of the $Do_2/\dot{V}o_2$ relationship over the very wide range of Do_2 values of patients who had ARDS. However, they suggested that the $Do_2/\dot{V}o_2$ relationship would best be determined using independent measurement of $\dot{V}o_2$ and Do_2 rather than applying a mathematical correction to dependent and independent terms which are mathematically coupled.[12] This is not taken into account in the studies considered in our analysis and hence, we believe that the great majority of reported results must be interpreted with caution.

"Supranormal" haemodynamics

Although several pioneering works[15,16] suggested that cardiovascular performance could influence the clinical behaviour of critically ill patients, the impact of these results was not particularly considered until Shoemaker and colleagues, approximately 20 yr ago, measured the physiological changes occurring in high-risk surgical patients.[17,18] They found median values in survivors to be a CI greater than 4.5 litre $\text{min}^{-1}\,\text{m}^{-2}$, Do_2 greater than 600 ml $\text{min}^{-1}\,\text{m}^{-2}$ and $\dot{V}o_2$ greater than 170 ml $\text{min}^{-1}\,\text{m}^{-2}$, and hypothesized that the greater values observed in survivors indicated physiological compensation for the increased metabolic requirements caused by the disease. They suggested that in high-risk surgical patients the increase in cardiac output and oxygen delivery could reduce mortality.

With time, this concept spread enthusiastically to different categories of critically ill patients, although considerable doubt has been cast on the value of this treatment concerning its ability to reduce morbidity and mortality, and its safety.

To date there are at least nine studies that qualify as randomized, controlled, clinical studies that specifically investigated if increasing oxygen transport in critically ill patients improves survival.[19–27] Three studies were performed in surgical patients,[19,21,26] two in trauma patients,[20,22] one in septic patients[27] and three in heterogeneous critically ill patients.[23–25]

Shoemaker and colleagues[26] evaluated the effects of increasing CI, Do_2 and $\dot{V}o_2$ in 88 surgical "high-risk patients" before operation, allocated randomly to one of three groups: two groups with normal haemodynamic targets and one group with a supranormal haemodynamic target. In the supranormal group they found: less complications (11 *vs* 39 and 31; $P<0.001$); lower percentage of patients with one or more complications (28% *vs* 50% and 50%; $P<0.05$) and shorter duration of ICU stay (10.2±1.6 days *vs* 15.8±3.1 and 11.5±1.7 days; $P<0.05$). Mortality rates were 23% and 33% in the two groups with normal haemodynamic targets and 4% in the group with supranormal haemodynamic targets ($P<0.05$).

Tuchschmidt and colleagues[27] evaluated the effects of increasing CO and Do_2 in 51 patients with septic shock allocated randomly to either a "normal treatment" (NT) or "optimal treatment" (OT) group. Mortality rate was 72% in the NT group and 50% in the OT group ($P=0.14$).

Fleming and colleagues[22] evaluated the effect of increasing oxygen delivery in 67 trauma patients allocated randomly to either a control group ($n=34$) or a treatment group ($n=33$). The incidence of organ failure was significantly lower in treated patients (0.79±0.68 organ failures per patient *vs* 1.74±1.64; $P<0.05$) with a significantly lower duration of mechanical ventilation and ICU stay (4±2 *vs* 11±3 and 5±1 days *vs* 12±4 days, respectively; $P<0.05$ for both). The observed mortality rate was 24% (eight of 33 patients) in the treatment group and 44% (15 of 34 patients) in the control group ($P=0.08$).

Yu and colleagues[25] examined the effects of increasing Do_2 in 67 critically ill patients prospectively, allocated randomly to a control group or treatment group. There was no significant difference between the two groups in development of organ failure, duration of ICU and hospital stay or mortality (34% in the two groups).

Boyd, Grounds and Bennet[21] evaluated the effects of increasing Do_2 in 107 high-risk surgical patients, allocated randomly to a treatment group ($n=53$) or control group ($n=54$). They found no significant difference in duration of hospital or ICU stay although a significantly lower number of complications per patient (0.48±0.10 *vs* 0.93±0.19; $P=0.008$) and a significantly lower mortality (5.7% *vs* 22.2%; $P=0.015$) were observed in the treatment group.

The study of Hayes and colleagues[24] was of a heterogeneous critically ill population, allocated randomly to a treatment or control group and was interrupted after the randomization of 100 patients (50 *vs* 50) as the treated patients showed a statistically significant higher mortality (25/50 *vs* 15/50; $P<0.05$). There was no difference in duration of mechanical ventilation or ICU stay between the two groups.

Bishop and colleagues[20] measured the effects of increasing CI, Do_2 and $\dot{V}o_2$ in 115 patients with severe trauma, allocated randomly to a control or treatment group. Duration of mechanical ventilation and ICU stay were significantly shorter in the treatment group compared with the control group (4±1 *vs* 9±1 and 6±1 *vs* 11±2 days, respectively; $P<0.05$ for both). The incidence of organ failure was significantly less in the treatment group than in the control group (0.74±0.28 *vs* 1.62±0.28 organ failure per patient, respectively; $P<0.05$). Nine of the 50 (18%) treated patients and 65 (37%) of the control patients died ($P=0.03$).

Berlauk and colleagues[19] tested the hypothesis that optimizing haemodynamics would improve outcome in patients undergoing limb-salvage arterial surgery: 45 patients had been haemodynamically optimized at least 12 h before operation (group 1), 23 were optimized within 3 h of surgery (group 2) and 21 did not have optimization (group 3). Group 3 experienced a significantly higher incidence of intraoperative events compared with either group 1 ($P<0.05$), group 2 ($P<0.05$) or combined groups 1 and 2 ($P<0.05$). Mortality rate was 2.2% in group 1, 0% in group 2 and 9.5% in group 3 (1.5% for groups 1 and 2 *vs* group 3; $P=0.08$).

Finally, Gattinoni and colleagues,[23] in 1991, designed a randomized, multicentre study to assess the effects of goal-oriented haemodynamic therapy in an unselected population of critically ill patients. Patients enrolled in the study were allocated randomly to one of three different haemodynamic targets: normal values of CI ($2.5 \le CI \le 3.5$ litre min^{-1} m^{-2}) (group I), supranormal values of CI (CI >4.5 litre min^{-1} m^{-2}) (group II) and mixed venous oxygen saturation ($S\bar{v}_{O_2}$) greater than 70% or a difference of less than 20% between arterial oxygen saturation and $S\bar{v}_{O_2}$ (group III). A total of 252 patients were assigned to group I, 253 to group II and 257 to group III. There were no differences in mortality between groups I, II and III at discharge from the ICU (48.4%, 48.6% and 52.1%, respectively; $P=0.638$) or at 6-months follow-up (62.3%, 61.7% and 63.8%, respectively; $P=0.875$). The three haemodynamic protocols did not affect the morbidity of the surviving patients who had a similar incidence of organs failure at the end of the 5-day study ($P=0.660$) and a similar duration of stay in the ICU (25.5±49.5 days for group I; 21.6±20.3 days for group II; 24.3±26.9 days for group III; $P=0.502$).

In summary, in the three studies which assessed the effects of increasing either Do_2 or $\dot{V}o_2$ in high-risk surgical patients,[19 21 27] mortality was decreased in two[21 26] and unchanged in one.[19] This reduction in mortality was observed only when supranormal haemodynamic targets were applied as a "preventive manoeuvre". In severe trauma, two studies[20 22] reported a decrease in mortality in supranormally treated patients although the difference was statistically significant only in the larger study.[20] No significant improvement in mortality with the use of supranormal haemodynamic targets was reported either in the two studies which included patients with sepsis and/or adult respiratory distress syndrome[25 27] or in the two studies of unselected critically ill patients.[23 24]

Conclusion

Factors such as patient age, chronic health status and severity of acute illness can contribute to the response to treatment. This is especially true in critically ill patients where such factors may be predominant in determining outcome, so that the effects of any therapeutic intervention on outcome may become less evident. In the case of supranormal haemodynamic targets, several studies showed that critically ill patients with normal or supranormal haemodynamic values were more likely to survive than those with less than normal haemodynamic values. Others showed that survival after trauma, surgery or sepsis is associated with attainment of high levels of oxygen delivery and consumption. Since a cause–effect relationship between the two phenomena has not been formally found, it may be that the ability of the patients to respond to manipulations of haemodynamics rather than the results of those manipulations that could account for the observed improvement in survival. This conclusion was supported by the Jury of the 3rd European Consensus Conference in Intensive Care Medicine held in December 1995 at Versailles, France[28] which examined the existing literature either on an intent-to-treat basis or according to achievement of supranormal haemodynamic values. This *post hoc* analysis suggested that although mortality was decreased in a subset of patients who achieved, and perhaps maintained, supranormal haemodynamic values, an intent-to-treat analysis showed no decrease in mortality among unselected groups of patients randomized to supranormal haemodynamic values.

There may be benefits in setting supranormal haemodynamic targets before operation in selected groups of patients, but there is no evidence to date to support the routine use of this approach in unselected groups of critically ill patients.

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Preoperative packed cell volume necessary for patients undergoing elective surgery

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Clinicians have struggled with determining the appropriate "trigger" for transfusing patients, ever since the concept was introduced more than 50 yr ago. Several candidates have been considered as triggers, including haemoglobin/packed cell volume, oxygen variables, symptoms and metabolic products. This brief review focuses on the use of haemoglobin/packed cell volume as transfusion triggers in elective surgical patients. Information has been obtained from a variety of sources, including animal experiments, retrospective reviews of anaemic patients and studies of transfusion in selected groups of patients.

Haemoglobin as part of a physiological basis for transfusion

Oxygen delivery is a function of both cardiac output and arterial oxygen content (table 1). Arterial oxygen content is dependent on both haemoglobin concentration and the percentage of oxygen carried by the haemoglobin molecule, or saturation. Oxygen dissolved in plasma contributes a negligible amount to overall delivery. Under normal, resting circumstances, the heart delivers 2–4 times the amount of oxygen consumed at the tissue level. With a haemoglobin concentration of 15 g dl^{-1}, an oxygen saturation of 99% and oxygen exchange of 5 litre min^{-1}, oxygen delivery is approximately 1000 ml min^{-1}. Whole body oxygen consumption is typically 200–300 ml min^{-1}. Oxygen consumption remains constant and is independent of delivery until the critical threshold, which varies for each organ system, has been reached. A composite threshold value of 4–10 ml min^{-1} kg^{-1} can be estimated from several clinical and laboratory studies.[1]

This critical level of oxygen consumption is approached when haemoglobin concentration decreases to 5 g dl^{-1}, assuming that all other variables remain constant. Below this value for oxygen delivery, and by extension of haemoglobin concentration, oxygen consumption becomes delivery dependent. Hoeft and colleagues have developed a theoretical model that describes these relationships and the importance of haemoglobin concentration.[2] Their work places the "permissive" haemoglobin concentration acceptable for a critical degree of intentional haemodilution at 4.7 g dl^{-1}. They postulate that any increases in oxygen consumption, such as those seen in the immediate postoperative period, require higher haemoglobin values to maintain acceptable oxygen delivery.

In most clinical settings, oxygen consumption is relatively independent of haemoglobin concentration across a wide range of oxygen delivery values because of compensations in oxygen extraction. As delivery decreases through loss of haemoglobin, oxygen extraction should increase from a baseline of 15–25% to maintain constant consumption.[3] Any increase in circulating volume that improves cardiac output also mathematically improves oxygen delivery, regardless of haemoglobin concentration. However, an improvement in delivery does not necessarily lead to an increase in oxygen consumption. Wilkerson and co-workers have shown in the exchange-transfused baboon that oxygen consumption is maintained to a packed cell volume of 4% through an increase in oxygen extraction ratio.[4] Addition of an experimental coronary stenosis in this model results in depressed cardiac function at haemoglobin concentrations of 7–10 g dl^{-1}. The investigators detected a conversion to anaerobic metabolism at a packed cell volume of 10% which correlated with an oxygen extraction ratio of 50%, suggesting these two values may be useful as transfusion guidelines.

The heart provides the primary response to acute, normovolaemic anaemia by increasing cardiac output, either by an increase in stroke volume or an increase in heart rate, or both.[3 5] As packed cell volume decreases, blood viscosity decreases, leading to an increase in venous return or augmentation of preload. Increases in heart rate are thought to be caused by stimulation of aortic chemoreceptors and release of catecholamines. The ability of the heart to respond is affected by multiple factors, including underlying disease, the patient's overall condition, such as shock and volume status, and the types and amounts of medications given, including anaesthetics and beta-blocking agents.

As heart muscle extracts approximately 80% of oxygen delivered to it under normal conditions, its ability to increase output is limited by its ability to increase its own oxygen consumption. The combination of anaemia and cardiac disease may place impossible demands on the heart. Cardiac oxygen extraction is improved by increasing coronary flow. In the presence of coronary artery disease, the heart may be unable to dilate coronary arteries sufficiently to provide the work needed to increase total body

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Table 1 Oxygen transport variables

A. D_{O_2}=CO×Ca_{O_2}×10
D_{O_2}=oxygen delivery
CO=cardiac output
Ca_{O_2}=arterial oxygen content
B. Ca_{O_2}=% arterial saturation of Hb×1.34 (ml g^{-1})
×[Hb] (g $litre^{-1}$)+(0.003×dissolved arterial oxygen)
$C\bar{v}_{O_2}$=% venous saturation of Hb×1.34 (ml g^{-1})
×[Hb] (g $litre^{-1}$)+(0.003×dissolved venous oxygen)
C CO=HR×SV
HR=heart rate
SV=stroke volume
D. Oxygen consumption (V_{O_2})=CO×(Ca_{O_2}–$C\bar{v}_{O_2}$)×10
E. Oxygen extraction ration (O_2ER)=V_{O_2}/D_{O_2}

oxygen delivery without risk to the myocardium.[6] Under these conditions, coronary blood flow is shifted from the endocardium to the epicardium, producing a localized, anaerobic/ischaemic environment and eventual subendocardial infarction.[3,6] Critical levels of oxygen consumption are reached much earlier in the diseased heart in the presence of anaemia (fig. 1).

Early studies of the role of packed cell volume, cardiac function and oxygen transport have supported 10 g dl^{-1} as an optimal haemoglobin concentration. *In vitro* rheological studies of diluted blood pumped through glass tubes at constant pressure showed that oxygen delivery peaks at packed cell volume values of 30%, then declines with progressive haemodilution.[7] Oxygen transport and survival are maximized at packed cell volume values of 30–40% in the experimental animal.[8,9] Animal studies of normovolaemic haemodilution have shown that the lower limit of cardiac tolerance for anaemia is approximately 3–5 g dl^{-1} in the absence of underlying disease.[4,10] Clinical studies have shown that in healthy subjects, a target packed cell volume of 20–25% (haemoglobin 7.0–8.0 g dl^{-1}) is feasible and safe for the patient. Kreimeier and Messmer have demonstrated in humans that intraoperative target haemoglobin concentrations of ≤5.0 g dl^{-1} have been tolerated by surgical patients without adverse effects.[11] Studies in paediatric patients (1–8 yr) who underwent haemodilution with either hydroxyethyl starch or dextran in conjunction with major surgery showed that a decrease in packed cell volume to 17% (equivalent to a haemoglobin concentration of 5.6 g dl^{-1}) was well tolerated with no significant decrease in oxygen delivery and global tissue oxygenation.[12]

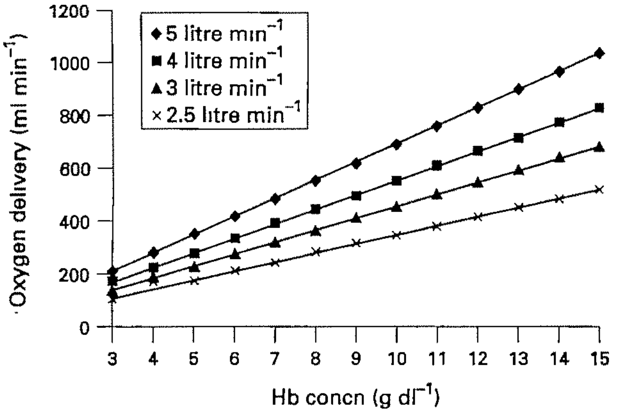

Figure 1 Effect of cardiac output (2.5, 3, 4 and 5 litre min^{-1}) and haemoglobin (Hb) concentration on oxygen delivery.

Peripheral tissues may also compensate for anaemia by increasing oxygen delivery, either by recruiting more capillaries or by increasing blood flow through existing beds.[1] Some tissues, particularly those that are supply-dependent, may compensate by increasing oxygen extraction.[13] In the chronically anaemic patient, increases in stroke volume and, therefore, in cardiac output, are supplemented by increased concentrations of 2,3 diphosphoglycerate (DPG). These intracellular changes shift the oxyhaemoglobin curve to the right, facilitating oxygen dissociation and increasing oxygen delivery.

Compensatory changes are similar in patients with chronic anaemia. Georgieva and Georgieva demonstrated alterations in both the microcirculation and heart in 299 female patients with severe iron-deficiency anaemia.[14] The majority of patients showed increased diameter and irregularity of the microcirculation. With lower haemoglobin concentrations, significant enlargement of the left ventricle and increased cardiac output and stroke volume were observed. A slight reduction in myocardial contractility was found only in those patients with severe anaemia. It is of interest that treatment with parenteral iron induced complete reversibility of both myocardial and microcirculatory changes in both moderate and minor iron-deficiency anaemia.

Some current policies focus on the use of haemoglobin as part of a physiological transfusion decision, stating that blood should be transfused *only* when there is a documented need to increase oxygen delivery in those patients who are unable to meet demands through normal cardiopulmonary mechanisms.[5,6,15] This statement is self-evident, as the primary function of red blood cells is the transport of oxygen to tissues. Therefore, any red cell transfusion should be physiological, to provide the additional oxygen delivery needed to correct, or protect, against the development of tissue hypoxia.[13] However, moving from theoretical triggers based on physiological variables to actual clinical practice is extremely difficult because of our inability to measure physiological changes without invasive and somewhat risky techniques. Sowade and colleagues' study of the role of recombinant human erythropoietin as an alternative to allogeneic transfusion used the Siggaard–Andersen oxygen status algorithm as an indicator of transfusion needs.[16] Farrell and Wasser presented a mathematical modelling approach to understanding changes in oxygen delivery and consumption.[17] Neither approach has been tested extensively in clinical practice; both may be useful in the intensive care unit where oxygenation data and computers are readily available. These approaches, which incorporate frequent measurements of haemoglobin, oxygen and cardiopulmonary variables that are fed into the algorithm, may be the way of the future. By gathering multiple data points, weighting them and analysing them with a computer program, we may be able to make better informed transfusion decisions.

Haemoglobin as a transfusion trigger

In clinical practice, the degree of anaemia plays the most significant role in the transfusion decision in surgery, as most patients are transfused based on isolated haemoglobin and packed cell volume values.[18–20] The National Institutes of Health consensus conference, convened in 1988 to address the topic of perioperative red cell transfusion, focused primarily on the risks of transfusion and the need to modify our transfusion practices.[21] It also produced recommendations for a new transfusion trigger that represented an update over the traditional 10/30 rule (haemoglobin/packed cell volume) that had existed for years.[22] The target, or trigger, haemoglobin was lowered to 8 g dl^{-1} and guidelines for transfusion were given that directed attention towards assessment of clinical need and symptoms rather than values alone.

Two concepts form the basis for the use of haemoglobin as a transfusion trigger—the optimal haemoglobin/packed cell volume and the minimally acceptable haemoglobin/packed cell volume. For many years, they were considered to be one and the same. Before the early 20th century, when routine blood transfusion became possible, surgeons tolerated low haemoglobin concentrations because there was little that could be done to change them. By the 1930s, Carrel and Lindberg had demonstrated that isolated organs could survive and grow in an extremely anaemic environment, defining the minimally acceptable haemoglobin concentration for sustained life as approximately 3 g dl^{-1}.[23] During the ensuing years, as transfusion became a part of everyday practice, the optimal haemoglobin concentration was defined clinically. In 1941, less than 10 yr after the first blood bank opened, Adams and Lundy recommended that all patients with preoperative haemoglobin concentrations less than 10 g dl^{-1} should be transfused before surgery, basing this decision on their clinical experience and understanding of oxygen transport dynamics.[24] A few years later, Clark and colleagues[25] provided some clinical support for the 10 g dl^{-1} value when they proposed that patients with the anaemia of "chronic shock" would benefit from preoperative transfusion. The 10 g dl^{-1} haemoglobin concentration, or the "10/30" rule for transfusion soon became a doctrine that persisted for many years.

Several studies designed to establish an optimal haemoglobin value noted that lower concentrations were tolerated by most patients. Clinical studies yielded further information regarding the minimally acceptable haemoglobin concentration in the form of mortality and morbidity data in anaemic surgical patients, many of them non-transfused Jehovah's Witnesses. Lum concluded that the mortality rate in 1584 anaesthetized surgical patients was inversely correlated to haemoglobin concentration.[20] However, this study did not assess or control for other factors that have an effect on survival: concurrent medical problems or type of surgical procedure. Furthermore, mortality rates were not given for haemoglobin concentrations less than 10 g dl^{-1}, making it impossible to assess the effect of severe anaemia on the risk of death. In Rawstron's comparison of 145 patients with preoperative haemoglobin concentrations less than 10 g dl^{-1} with a group of 412 surgical patients with haemoglobin concentrations ≥10 g dl^{-1}, the number of postoperative complications was similar.[26] However, both groups received preoperative transfusion, which may have obscured a difference in operative risk. Outcomes were not stratified for haemoglobin concentrations less than 10 g dl^{-1}. Alexiu and colleagues compared postoperative mortality and morbidity in patients with gastrointestinal bleeding.[27] Sixty-nine transfused patients were compared with 72 who were resuscitated with large volumes of glucose and 0.9% sodium chloride solution. In patients not given blood, mean preoperative packed cell volume was 29% (range 16–42%), which decreased by the second day after operation to a mean of 23.3% (range 10–37%). There was no mortality and the complication rate was lower than in the transfused group. However, the number of patients with haemoglobin concentrations less than 10 g dl^{-1} was not stated and the presence of potentially confounding medical problems was not included. Data from a long-term study of 811 male patients who underwent transurethral prostatectomy for benign prostatic hypertrophy showed a correlation between a preoperative haemoglobin concentration of 10–12.9 g dl^{-1} and increased long-term risk of acute myocardial infarction. The authors adjusted their data for impaired health status, age greater than 75 yr, fluid absorption and blood loss, although the associations and their relative effect were unclear.[28]

Several studies of anaemia and the risk of postoperative morbidity and mortality in Jehovah's Witnesses have been reported.[29 30] Spence and colleagues studied 125 patients undergoing either emergency or elective surgery. Mean preoperative haemoglobin concentration in those who died was 7.6 g dl^{-1} and was significantly lower than that in survivors (11.8 g dl^{-1}; $P<0.002$). Patients with preoperative haemoglobin concentrations of 0–6 g dl^{-1} had a mortality rate of 61.5%, for a haemoglobin concentration of 6.1–8 g dl^{-1}, mortality rate was 33.3%, for a haemoglobin concentration of 8.1–10 g dl^{-1}, mortality was 0% and for a haemoglobin concentration ≥10 g dl^{-1}, mortality rate was 7.1%. No patient with a preoperative haemoglobin concentration >8 g dl^{-1} and operative blood loss less than 500 ml died (upper 95% confidence interval, 5%). However, the study was too small to describe precisely the risk of death in patients with haemoglobin concentrations of 6–10 g dl^{-1}. A subsequent analysis of 113 elective operations in 107 Jehovah's Witness patients showed that mortality was 0% with haemoglobin concentrations as low as 6 g dl^{-1} as long as blood loss was kept less than 500 ml.

The minimally acceptable haemoglobin value may be that beyond which coronary artery blood flow cannot increase enough to meet myocardial oxygen demands, but this concentration has yet to be defined clinically. Czer and Shoemaker determined that an optimal packed cell volume of 33% was desirable in critically ill patients, but emphasized the importance of maintaining adequate volume status over transfusion.[9] Their patients had acute blood loss from trauma or had undergone emergency surgery. Haemoglobin concentrations were confounded in their analysis by both the nature of the critical illness and volume replacement. Even so, patients with normal compensatory mechanisms tolerated packed cell volume concentrations as low as 18%. These investigators subsequently demonstrated maintenance of both cardiac output and oxygen consumption in dogs with packed cell volumes as low as 10% as long as circulating volume remained normal. In our study of mortality and haemoglobin concentration in Jehovah's Witnesses, preoperative cardiac disease, as defined by the multifactorial cardiac risk index, appeared to worsen outcome.[30] In a smaller study of 47 patients with more severe anaemia (mean haemoglobin 4.6± 0.2 g dl^{-1}), a history of cardiac, pulmonary or renal disease had no association with adverse outcome.[31] An increased incidence of electrocardiographic evidence of myocardial ischaemia in postoperative vascular patients with packed cell volumes less than 29% was found by two separate investigators.[32 33] In a retrospective, cohort study of 1958 adult Jehovah's Witnesses, Carson and colleagues demonstrated that the non-transfused Jehovah's Witness patient with cardiopulmonary disease is at increased risk of dying as haemoglobin decreases to less than 10 g dl^{-1}.[34]

Optimization of cardiopulmonary haemodynamics should precede red blood cell transfusion.[5] Supranormal oxygen delivery and improved haemodynamics can be achieved in many patients by a variety of means, including increasing inspired oxygen, fluid infusions to increase preload and the use of inotropes. Such interventions are more likely to be successful in those patients aged less than 50 yr and with good cardiac function.[1] Robertie and Gravlee recommended a transfusion trigger of 6 g dl^{-1} in well-compensated patients with no heart disease and no postoperative complications.[7] A higher trigger (8 g dl^{-1}) should be used in patients with stable cardiac disease and when blood loss of approximately 300 ml is expected. Older patients and those with postoperative complications who cannot increase cardiac output to compensate for haemodilution should be transfused when haemoglobin concentration reaches 10 g dl^{-1}.

Effect of transfusion on outcome

Information is slowly appearing on the benefits of transfusion in both surgical and intensive care patients. Most studies have examined either cardiac morbidity or overall mortality as outcomes. Hébert and colleagues summarized several studies that have been conducted to evaluate the effect of transfusion on oxygen transport in the critically ill patient.[36] Pre-transfusion oxygen extraction ratios were 0.24–0.48, with the highest values seen in patients with cardiogenic shock. The effect of transfusion to a haemoglobin concentration of 10 g dl^{-1} on oxygen extraction ratio was minimal in most patients. Hébert and colleagues published the results of two studies addressing the value of transfusion in critically ill patients. A combined retrospective and prospective cohort analysis of 4470 patients admitted to intensive care units with a variety of diagnoses showed that anaemia increased the risk of death in critically ill patients and that blood transfusion appeared to decrease this risk.[36]

Unfortunately, the evidence for either benefit from red blood cell transfusion or for a clearly defined transfusion trigger remains elusive. A multicentre, randomized, controlled pilot study of two transfusion triggers (one restrictive, 7–9 g dl^{-1}; one liberal, 10–12 g dl^{-1}) in the treatment of similar patients showed no difference in ICU 30-day and 120-day mortality.[37] A recent meta-analysis of clinical studies designed to maximize oxygen delivery in ICU patients by increasing variables to supranormal levels was unable to demonstrate any reduction in mortality rate.[38] Bush, Pevec and Holcroft obtained similar results in their prospective, randomized study of two treatment strategies designed to test the 10 g dl^{-1} transfusion trigger in vascular surgical patients.[39] Ninety-nine patients undergoing elective aortic and infrainguinal arterial reconstructions were randomized prospectively before operation to receive transfusions to maintain a haemoglobin concentration of either 9 or 10 g dl^{-1}. There were no significant differences in mortality or cardiac morbidity rates, duration of hospital stay or oxygen consumption between the two groups. The study of Carson and colleagues of 8787 patients treated as emergencies for hip fractures showed no benefit from transfusion on either 30-day or 90-day mortality.[40] Unfortunately, 90.5% of patients with haemoglobin concentrations less than 8 g dl^{-1} were transfused, thereby limiting the usefulness of these findings. An extensive review of all the relevant clinical literature on transfusion studies, risks and benefits found no conclusive evidence of benefit from red blood cell transfusion.[42]

What is the impact of red cell transfusion on cardiac activity? As anaemia can jeopardize cardiac activity, transfusion should improve cardiac function. Few studies have been performed to study this question. Nelle, Hoecker and Linderkamp evaluated the impact of red blood cell transfusion on right ventricular function in 38 preterm infants with a mean gestational age of 28 weeks and birth weight of 1060 g, using pulsed-Doppler echocardiography.[42] The infants were studied at a mean postnatal age of 44 days. As expected, blood transfusion increased packed cell volume by 46%, haemoglobin from 8.2 to 12.8 g dl^{-1}, and blood viscosity by 33%. Right ventricular output decreased significantly as a result of a decrease in heart rate by 7%. Arterial pressure and right ventricular variables, including stroke volume, pre-ejection period, peak velocity and ejection time, did not change. In spite of this, there was a significant increase in pulmonary red cell oxygen transport of 21% because of the increase in packed red cell volume. These results suggest that neither pulmonary artery pressure nor right ventricular function changed as a result of transfusion in spite of increasing blood volume and blood viscosity. In other words, red cell transfusion had little impact on right heart activity other than by slowing overall heart rate. It is not known if these changes are characteristics of the neonatal circulation alone, or if they also occur in adults.

Even fewer studies on the relationship between pulmonary disease, haemoglobin concentration and the benefits of transfusion have been done. Intentional haemodilution experiments have given some idea of "how low we can go" with haemoglobin concentrations before getting into difficulties. Deem and colleagues studied the effect of normovolaemic anaemia in a rabbit model of isovolaemic haemodilution to determine if carbon dioxide elimination and retention were impaired with decreasing concentrations of haemoglobin.[43] Isovolaemic anaemia was induced by simultaneous blood withdrawal and infusion of 6% hetastarch in sequential stages; exchange transfusions ranged from 15 to 30 ml. Pa_{CO_2} remained stable between packed cell volume values of 36% and 12%, as a result of increases in both cardiac output (50%) and oxygen extraction ratio (61%). These data suggest that a 66% reduction in packed cell volume is tolerated well, with no adverse effect on pulmonary carbon dioxide gas exchange, as long as the mechanisms for oxygen delivery and extraction remain intact. A report by Schonhofer and colleagues demonstrated that the work of breathing is increased by anaemia in patients with lung disease.[44] These investigators transfused 21 anaemic (haemoglobin concentration <11 g dl^{-1}), male patients, 15 of whom had pulmonary disease, with 2–3 units of packed red blood cells to determine if correction of anaemia improved pulmonary function. Patients were studied 24 and 36 h after transfusion. In those patients with combined disease, an average of 2.2 red blood cell transfusions led to a 20% reduction in ventilatory effort, thereby reducing the work of breathing. Blood transfusion did not reduce the frequency of apnoea, bradycardia or hypoxaemia in 21 spontaneously breathing preterm infants with anaemia (median haemoglobin concentration 10.9 (82–120) g dl^{-1}).[45] The authors concluded that the occurrence of frequent episodes of apnoea, bradycardia and/or hypoxaemia did not, on its own, justify a blood transfusion in moderately anaemic preterm infants. These studies suggest that anaemia in patients with pulmonary disease may have an adverse effect and that red blood cell transfusion may improve pulmonary function, albeit temporarily.

Conclusion

The above studies show that a haemoglobin concentration significantly lower than 10 g dl^{-1} is tolerated by many patients. This does not necessarily mean that a *tolerable* haemoglobin concentration should automatically be considered an *acceptable* concentration for use as a transfusion trigger in all patients. Conversely, it is unnecessary and potentially risky to transfuse all patients to an optimal haemoglobin of 10 g dl^{-1}. The main problem with a haemoglobin-based trigger is its lack of general applicability. Some patients can tolerate very low perioperative haemoglobin concentrations while others will require supranormal values to survive, depending on diagnosis and clinical condition. Baron's report for the French Consensus Conference on haemodilution in cardiac surgery recommended that a postoperative packed cell volume of 25% is acceptable if the patient remains asymptomatic. Otherwise, the transfusion decision must include both packed cell volume and symptoms.[46] Current evidence supports this statement and points out the importance of considering both cardiac and pulmonary status, in addition to the underlying disease state, together with the haemoglobin concentration. There is no single, acceptable, preoperative packed cell volume that is safe for all patients.

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Management of preoperative anaemia

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The requirement for blood transfusion during surgery depends on two major variables: (1) the volume of perioperative blood loss, which is related to the type of surgery, the adequacy of surgical haemostasis and the surgical and anaesthetic techniques used; and (2) the volume of blood loss that the patient can tolerate before transfusion is indicated.

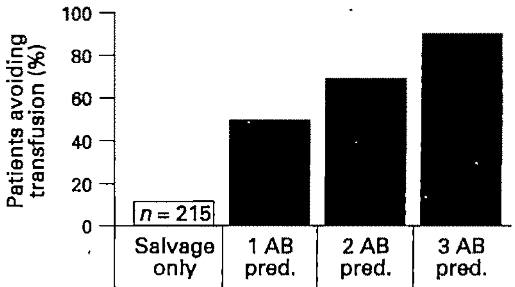
This second variable is affected mainly by the clinical condition of the patient, particularly by cardiopulmonary and haematological status, that is the total circulating red blood cell (RBC) mass. Low baseline packed cell volume has been shown to be a critical variable in affecting transfusion requirement. The incidence of preoperative anaemia is relevant in many categories of patients, but particularly in those with anaemia of chronic diseases (ACD).[1 2] Patients most affected by this type of anaemia are those with cancer and rheumatoid arthritis.[3 4]

Anaemia is common in cancer patients, especially in those with more advanced stages of progressive tumour growth,[5] and represents an important component of the morbidity related to the malignancy. Few data are available on the frequency of anaemia, however it has been reported that approximately 50% of patients with cancer are anaemic, the frequency varying with the type of cancer, stage, and chemotherapy or radiation therapy used.[3] The pathophysiology of the anaemia associated with malignancy is multifactorial and not completely understood. However, in the majority of cases ACD plays a major role.[1] The anaemia generally develops slowly and is usually mild to moderate in severity, with haemoglobin values in the range 8–10 g dl^{-1}.[3 6] However, especially in patients receiving chemotherapy, values can be ≤7 g dl^{-1}. It has been reported that the percentage of patients requiring transfusion ranges from 20% to 50%.[7–9] This incidence increases markedly when patients undergo cancer surgery: in a meta-analysis of 14 studies in colorectal cancer, it was calculated that allogeneic blood transfusion was given to 45–84% of subjects.[10]

Anaemia is one of the most frequently occurring extra-articular manifestations of rheumatoid arthritis. Although iron, vitamin B12 and folic acid deficiencies are quite prevalent, as indeed is the anaemia arising from complications during anti-rheumatic drug therapy, ACD is one of the major underlying causes of a low packed cell volume in these patients. The anaemia is usually mild and relatively well tolerated (generally no more than 10% of patients have severe anaemia).[11] However, when major orthopaedic surgery is required, anaemia can preclude collection from the patient of sufficient blood to cover their transfusion needs.

Low baseline packed cell volume values have also been found to be detrimental in surgical patients without underlying diseases undergoing elective orthopaedic surgery.[12] Indeed, it has been demonstrated that in patients enrolled in predonation programmes, inability to donate the optimal number of autologous units is the major cause of allogeneic transfusion (fig. 1).

The volume of blood that the patient can predeposit during the period before operation is a function of the total circulating RBC mass and the rate of recovery of packed cell volume after collection. A low baseline packed cell volume not only precludes the possibility of predonation when below 34%, but also significantly affects the quantity of blood that can be donated. For each unit of autologous blood (350–450 ml) collected, a mean decrease of 1 g dl^{-1} of haemoglobin and 3% of packed cell volume occurs. With collection of 3 units of blood, the packed cell volume is reduced by approximately 10% (fig. 2). Consequently, in a relevant percentage of patients with baseline packed cell volume less than 39–40%



	Salvage only	1 AB pred.	2 AB pred.	3 AB pred.
Blood loss (ml rbc)	630	620	643	782
HB units tranf.	2.48	1.23	0.43	0.22**
Baseline PCV	39.3	40.5	40.1	41.1
PCV 3 days postop.	28.2	26	28.3	28.3
PCV 7 days postop.	29.9	28.9	27.8	29.2

Figure 1 Percentage of patients avoiding homologous blood (HB) transfusion, mean perioperative blood loss, mean number of homologous blood units transfused and mean packed cell volume (PCV) values at baseline, 3 days and 7 days after surgery in 660 patients undergoing primary total hip replacement subdivided according to the number of autologous blood (AB) units predeposited (pred.). $P<0.05$

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the value decreases to less than 34% (threshold value for donation) after collection of the first or second donation. It has been estimated that anaemia precluded enrollment into the donation programme of 10% of surgical patients and limited the number of units collected in 31% of patients.[12]

To define the critical packed cell volume value below which patients would be at a higher risk of receiving allogeneic blood transfusion, we correlated the number of units actually predeposited by patients and the need to integrate autologous blood with allogeneic blood with the baseline packed cell volume value. We found that when baseline packed cell volume values were less than 37%, the blood that patients could predeposit (0–1 unit) was generally insufficient to cover their transfusion needs; when packed cell volume values were 37–40%, autologous blood donations covered transfusion requirements in approximately 56% of cases, and when packed cell volume values were greater than 40%, patients could predeposit 3 or more units of blood and were rarely exposed to the risk of transfusion with donor blood (fig. 3).[12]

To better define the distribution of baseline packed cell volume values in orthopaedic surgical patients, we analysed data from 2183 patients undergoing surgical procedures in the Orthopaedic Institute of the University of Milan. Patients were subdivided into different classes according to baseline packed cell volume values and the underlying disease requiring surgical intervention (table 1). Of 2183 patients, a total of 381 patients (18%) had a baseline packed cell volume lower than 34%, a value that prevents the use of preoperative autologous blood donation (PABD), a method of proven efficacy to reduce the use of allogeneic blood in surgical patients. Moreover, a total of 1010 patients (46%) had baseline packed cell volume values of 34–40% and were at high risk of allogeneic blood transfusion when undergoing major orthopaedic surgery with an expected transfusion requirement of 2–3 units. Only 792 patients (36%) had optimal baseline values (higher than 40%). As expected, the incidence of baseline packed cell volume values less than 34% was only 7% in patients whose underlying disease was osteoarthritis but increased to 25%, 30% and 42% in patients with rheumatoid arthritis, cancer or sepsis, respectively. In trauma patients, the incidence was 35%.

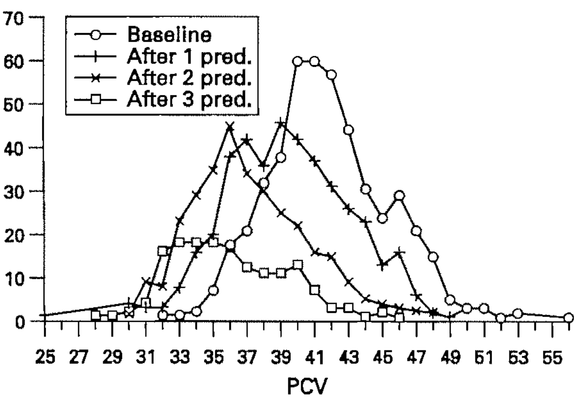

Figure 2 Distribution of packed cell volume (PCV) values in predepositing patients at baseline and after collection of the first, second and third predonated (pred.) autologous blood units.

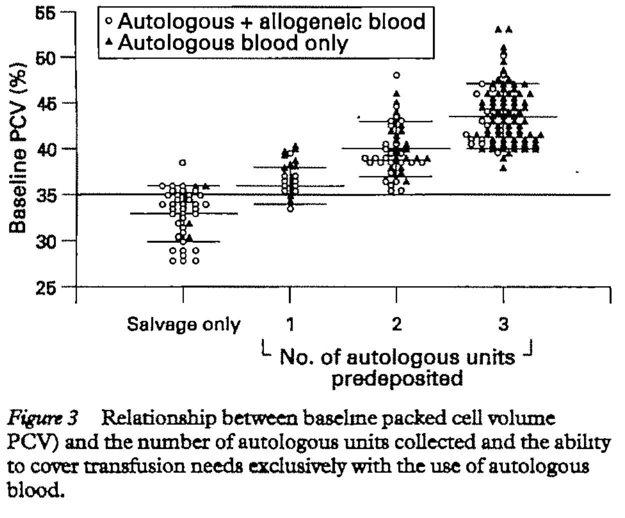

Figure 3 Relationship between baseline packed cell volume PCV) and the number of autologous units collected and the ability to cover transfusion needs exclusively with the use of autologous blood.

According to the analysis, a consistent proportion of patients undergoing major surgical procedures will not have their perioperative transfusion needs met exclusively by the use of autologous blood obtained using the currently available autotransfusion techniques (PABD and acute normovolaemic haemodilution (ANH)). In these patients, administration of recombinant human erythropoietin (rHuEPO) may be a valuable adjunct to increase the efficacy of all autotransfusion techniques.[13 14]

Several studies have evaluated, in different groups of patients, the efficacy of rHuEPO in enhancing collection of autologous blood in patients for elective surgery, in correcting anaemia before surgery and in accelerating the postoperative erythropoietic response, thus reducing the use of allogeneic blood.[15–20] In all clinical studies considered, rHuEPO was found to be effective in stimulating erythropoiesis and increasing new RBC production (although this was found to vary considerably (250–900 ml)) and the number of units predeposited. It was also effective in correcting anaemia induced by blood collection.[21 22]

The increase in the amount of blood deposited correlated well with the dose of rHuEPO administered.[23] The most common treatment procedure used involved i.v. administration, twice weekly for 3 weeks, together with oral iron supplements. Total doses of less than 600 iu kg^{-1} were ineffective in promoting sufficient erythropoiesis to significantly increase the volume of predeposited blood. Higher doses yielded a dose-dependent production of new RBC, ranging from 250 ml for total doses of 600 iu kg^{-1} to more than 900 ml for doses of 3600 iu kg^{-1}. It should be noted that, despite oral iron supplementation, the effect of rHuEPO therapy in autologous donors is very often restricted by iron depletion.[24–26] I.v. iron administration results in a better iron supply for erythropoiesis, with either an increased haemoglobin response to the same dose of rHuEPO or a reduction in the dose of rHuEPO required. With the use of i.v. iron sucrose, RBC regeneration and the volume of predeposited blood were identical when total rHuEPO doses of 1800 and 3600 iu kg^{-1} were compared.[15] The effectiveness of the subcutaneous route for rHuEPO has been shown in several studies.[26–28] In our experience (fig. 4), rHuEPO s.c. combined with i.v. iron was highly effective in autologous blood

Table 1 Distribution of baseline packed cell volume (PCV) in orthopaedic surgical patients operated on at the Gaetano Pini Orthopaedic Institute in 1997

	Baseline PCV				
	20.5–29.9%	30–33.9%	34–39.9%	40–55.9%	Total
No.of pts	129	252	1010	792	2183
(% of total)	(6)	(12)	(46)	(36)	
Female	99	203	831	389	1522
	(6.5%)	(13.3%)	(54.6%)	(25.6%)	
Male	30	49	179	403	661
	(4.5%)	(7.5%)	(27%)	(61%)	
Osteoarthritis	19	70	624	585	1298
	(1.5%)	(5.5%)	(48%)	(45%)	
Rheumatoid arthritis	6	16	42	19	82
	(7%)	(18%)	(52%)	(23%)	
Cancer	14	17	39	33	103
	(14%)	(16%)	(38%)	(32%)	
Sepsis	8	16	17	16	57
	(14%)	(28%)	(30%)	(28%)	
Trauma	78	126	264	113	581
	(13%)	(22%)	(45%)	(20%)	
Other	4	8	24	26	62
	(6%)	(13%)	(39%)	(42%)	

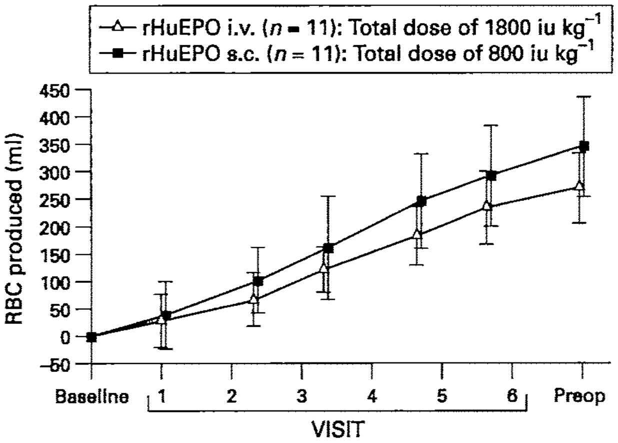

Figure 4 Production of new red blood cells (RBC) in patients treated with i.v. rHuEPO at a total dose of 1800 iu kg^{-1} and in those treated with s.c. rHuEPO at a total dose of 800 iu kg^{-1}. Both groups received i.v. iron supplementation.

donation and, compared with i.v. administration, resulted in a marked reduction (approximately 55%) in total rHuEPO dose.[27]

Recently, some studies have also evaluated the role of rHuEPO in those subgroups of patients for whom preoperative autologous blood donation is not feasible.[29] These include patients with anaemia or other disorders precluding donation, patients with limited time before surgery, and those who are unwilling to participate in an autologous blood donation programme because of logistical problems or religious beliefs. For example, postponing the operation in cancer or heart patients might be more detrimental than receiving allogeneic blood transfusion. In one study,[30] three different doses of rHuEPO were used (3000, 6000 and 9000 iu kg^{-1} i.v. 3 times a week for 2 weeks before and after surgery) combined with i.v. iron treatment. In a later prospective, placebo-controlled, double-blind study,[32] two different doses of rHuEPO (300 and 150 iu kg^{-1}) were administered s.c. for 8 consecutive days during the perioperative period (from day −5 to day +2). A reduced transfusion requirement was evident in both studies.

Perioperative use of rHuEPO in patients undergoing elective hip replacement reduced the portion of patients requiring transfusion from 74% to 33% when their baseline haemoglobin concentration was less than 13.5 g dl^{-1}.[32] Two additional studies have shown a significant reduction in transfusion rates with perioperative use of rHuEPO in subjects undergoing orthopaedic surgery with baseline haemoglobin concentrations of 10–13 g dl^{-1}.[33 34]

A short-term peroperative treatment regimen was used in a pilot study at our institute. Sixteen patients for whom predeposit was contraindicated for various clinical reasons and who were about to undergo major orthopaedic surgery with predicted transfusion requirements of 2–3 units of blood were enrolled in the study. The study involved s.c administration of rHuEPO at a daily dose of 100 iu kg^{-1} beginning 4 days before surgery up to the second day after surgery. On the first day of treatment, one 200 iu kg^{-1} bolus was also administered i.v. I.v. iron sucrose was administered concomitantly at a total dose of 600–1000 mg, according to baseline iron reserve values. The treatment produced a 2–7% increase in packed cell volume, with a mean increase in circulating RBC mass of 100 ml (from 0 to 245 ml) before surgery. Twelve of the 16 patients did not require allogeneic transfusion, whereas a total of 6 units of blood were transfused in the remaining four patients.[35] Although preliminary, these findings suggest that rHuEPO administration together with i.v. iron during a preoperative period of 4–5 days can stimulate erythropoiesis significantly, expand the circulating red cell mass and reduce transfusion requirements in patients who, for clinical or logistic reasons (heart surgery and cancer patients) are not able to deposit autologous units before elective surgery. Because of the short time period, this treatment could also be offered to a proportion of accident patients about to undergo surgery, when surgery was planned 4–5 days after injury.

Finally, rHuEPO administration has been investigated in surgical patients with ACD. In a pilot study carried out in our centre, 11 rheumatoid arthritis patients undergoing major orthopaedic surgery were selected for their inability to donate blood for autologous use because of anaemia (packed cell volume <34%) and received rHuEPO 300 iu kg^{-1} in combination with i.v. iron sucrose (100 mg of elemental iron) twice a week for 3 weeks.[36] Treatment was compared with that of 12 control patients with anaemia of comparable severity. The study demonstrated the safety and efficacy of rHuEPO in stimulating erythropoiesis, allowing preoperative donation of blood for autologous use and reducing exposure to allogeneic blood in anaemic rheumatoid arthritis patients. Indeed, control patients could not deposit any blood before operation for autologous use, while all but one of the rHuEPO treated patients deposited 2 or more units. The control group received more allogeneic units than control patients (mean 2.6±1.6 *vs* 0.8±0.8; $P=0.009$). Moreover, 50% of rHuEPO treated patients compared with 8% of controls completely avoided allogeneic transfusion.

Recombinant EPO has been shown to be effective in combination with autologous blood donation in patients undergoing transurethral resection for prostatic cancer.[37] Of the 266 patients who took part in the study, 134 predeposited blood. The rate of allogeneic blood transfusion was 6.7% in this group compared with 14.7% among patients who did not donate autologous blood before operation. Furthermore, in six patients who received concomitant rHuEPO therapy during preoperative autologous blood donation, the reduction in haemoglobin concentration during the predonation period was significantly less than among untreated patients (–0.4 *vs* –1.9 g dl^{-1}; $P<0.05$). Another study involved inclusion of rHuEPO (150 iu kg^{-1} s.c. three times weekly) into the intensive neoadjuvant chemotherapy regimen of 15 patients with sarcomas, to prevent the development of anaemia and allow preoperative autologous blood donation.[38] Twelve patients with identical neoadjuvant chemotherapy acted as controls. In total, 14 rHuEPO treated patients (93%) donated autologous blood; one patient could not donate because of severe iron-deficiency anaemia. No patient in this group required blood transfusion during chemotherapy, compared with eight patients (67%) in the control group. Hence, rHuEPO was found to be effective in reducing the incidence of anaemia and transfusion frequently associated with intensive chemotherapy. In addition, treatment with rHuEPO allowed patients to donate autologous blood before operation, thereby reducing the risk of exposure to allogeneic blood.

Because of the high cost of rHuEPO treatment, its routine use is unlikely to be cost-effective. To better select those patients who are most likely to benefit from this treatment, we defined a more personalized approach to calculate the expected transfusion needs for each patient.[39] This approach takes into account the two variables that affect the patient's transfusion requirement: perioperative blood loss and the volume of blood loss that the patient can tolerate before blood transfusion is indicated. Perioperative blood loss calculated in terms of red cell loss, by the circulating RBC volume (C-RBC-V) reduction from before surgery to a determined postoperative time (day 5 after operation in orthopaedic surgery), in addition to the volume of RBC transfused during this period, according to the following formula:

perioperative RBC loss (ml of RBC)=$\text{C-RBC-V}_{\text{presurgery}}-\text{C-RBC-V}_{\text{postop}}$+ml of RBC transfused,
where C-RBC-V (circulating RBC volume)=predicted blood volume (PBV)×packed cell volume.

When the total RBC loss for each patient is known, the mean, median or the appropriately selected percentile value of the distribution can be calculated for each procedure and surgical team performing it, and used as the predicted surgical red cell loss. In our centre, we decided to consider expected blood loss as the 80th centile of the distribution.

The volume of blood loss that the patient can tolerate depends on the baseline circulating red cell mass (that in turn depends on baseline packed cell volume and body weight) and the circulating red cell mass that gives a packed cell volume compatible with the clinical and cardiocirculatory condition of the patient (21–24% of packed cell volume for young patients in good general condition; 27–30% for elderly patients or those with cardiovascular or respiratory diseases), according to the formula: tolerated blood loss (ml of RBC)=

$(\text{PBV}\times\text{PCV}_{\text{baseline}})-(\text{PBV}\times\text{PCV}_{\text{min accepted}})$,
where PBV=predicted blood volume and PCV=packed cell volume.

The difference between predicted blood loss and tolerated blood loss is the transfusion requirement of the patient, expressed in ml of red blood cells. When a negative value is obtained, it means that the patient can tolerate a larger volume of blood loss than is expected to be induced by the surgical procedure. When a positive value is obtained, this represents the transfusion requirement (ml of red blood cells).

We retrospectively applied the algorithm to 577 patients, each of whom predonated 2 or 3 units of autologous blood before total hip replacement surgery, and subdivided the patients according to the calculated transfusion requirement (table 2). In patients with a calculated transfusion need greater than 500 ml of red blood cells (representing less than 5% of total evaluated patients), in spite of the use of all the currently available autotransfusion techniques, only 68% avoided the use of allogeneic blood. However, the incidence was more than 95% in patients with a calculated transfusion needing less than 200 ml of red blood cells. In this group of patients with a low calculated transfusion requirement, over-collection of autologous blood has been documented, as shown by the wastage of approximately 20% of the autologous units collected.

If we had applied the algorithm for the choice of the most appropriate blood conservation strategies, we would have avoided unnecessary collection of autologous blood in patients with low transfusion requirements, thus saving resources that could have been used for rHuEPO treatment in patients at higher risk of requiring allogeneic blood transfusion because of low baseline packed cell volume values.

Table 2 Transfusion results in 577 patients operated on for total hip replacement subdivided according to expected transfusion requirements calculated using the algorithm[*]. AB = Autologous blood

	Transfusion requirements (ml)						
	<0	0–100	100–200	200–300	300–400	400–500	>500
No. of pts (% of total)	50 (8.7%)	48 (8.3%)	67 (11.6%)	90 (15.6%)	139 (24.1)	156 (27%)	27 (4.7)
% Male	98	93	77	36	6.5	1.3	0
Units predeposited (unit/pt)	103 (2.0)	109 (2.2)	155 (2.3)	230 (2.5)	355 (2.5)	372 (2.4)	64 (2.4)
Units not transfused	20 (19.4%)	21 (19.2%)	29 (18%)	33 (12%)	28 (8%)	19 (5%)	0 (0%)
Pts transfused only autologous	98%	98%	95%	85%	82%	80%	68%
Pts with discarded units	16 (32%)	16 (33%)	22 (32%)	26 (28%)	25 (18%)	17 (11%)	0 (0%)
Pts transfused with all AB units with postop. PCV<27%	7 (14%)	9 (18%)	10 (15%)	22 (24%)	51 (37%)	74 (47%)	18 (66%)

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Methods for reduction of perioperative bleeding

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Surgical bleeding is the main cause of anaemia in the perioperative setting particularly in the elderly.[1] Perioperative blood loss varies with the underlying pathology, surgical expertise and the nature of surgery, and may cause anaemia or worsen pre-existing anaemia. A reduction in oxygen carrying capacity can cause profound physiological changes in the cardiovascular system. In all anaemic patients, but particularly in those with cardiovascular disease, such as congestive heart failure, ischaemic heart disease or peripheral vascular disease, anaemia increases perioperative mortality and morbidity.[2–4]

Controversy and uncertainty about the treatment of anaemia in perioperative and ICU patients are reflected in several reports on inappropriate transfusion practice, even in leading academic institutions.[5–7] Rather than blood transfusion, specific treatment with iron, B_{12}, folic acid or erythropoietin is recommended, if the clinical circumstances permit sufficient time for these agents to promote erythropoiesis. Blood conservation techniques may maintain red cell mass or reduce blood loss, or both, and thus reduce allogeneic transfusion requirements, but they may increase the risk of anaemia. Transfusion triggers are difficult to determine, and transfusion of allogeneic red cells, although now much safer because of screening, may not necessarily improve outcome.[8] For patients with a haemoglobin concentration of 8 g dl^{-1} or greater, transfusion of red cells does not appear to decrease the risk of morbidity and mortality after either 30 or 90 days, although patients are exposed to the risk of allogeneic blood transfusion.[2]

Some surgical blood loss is inevitable, but reduction of blood loss is vital to avoid perioperative anaemia and reduce morbidity and mortality in surgical patients.[9] Awareness of complications that can increase bleeding, skilful surgery combined with saving methods, reducing diagnostic and interventional blood loss and careful management of blood coagulation can reduce perioperative blood loss. Each strategy is valuable, but they are best used in combination.[10]

Monitoring blood loss

The clinician should assess the blood loss that can be tolerated by the individual patient. Direct estimation of actual blood loss by weighing swabs and by measuring the volume in suction is unreliable because swabs may become dry, suction volume diluted and, more important, haematoma or haemolysis is not considered. Although a decrease in haemoglobin concentration and the volume transfused do not strictly indicate blood loss, they reflect the patient's physiological response to haemorrhage. Using those variables for computer assisted mathematical calculations, blood loss can be estimated indirectly. Although variations in blood volume and fluid balance influence this estimate, computer simulations have shown these to be of minor importance.[11] Brecher, Monk and Goodnough found a strong relationship between directly estimated and indirectly calculated blood loss, but calculated blood loss was on average 2.1 times the intraoperative blood loss estimated by the anaesthetist.[12] The clinical use of such calculations is not clear, but in contrast with direct estimation, they may help to establish future standards for acceptable blood loss in certain procedures.

Diagnostic blood loss

Frequent blood sampling can cause anaemia and is a major factor contributing to red cell transfusion in the perioperative and ICU setting.[13 14] For example, an average of 65 ml per day is sampled in adult ICU patients, approximately 30% of the total red blood cells transfused.[14–16] In small adults and children, diagnostic blood loss becomes more serious and may be the same as the red cell volume transfused.[17 18] By recognition of frequent, often unnecessary, blood sampling by documenting diagnostic blood samples, altering test ordering behaviour, using small volume (paediatric) samples, eliminating arterial line blood discard and by using point of care diagnostics, diagnostic blood loss can be reduced.[14 15 19–22]

Surgical technique

In addition to the surgical procedure, the quality of the surgical technique accounts for a large part of the variation in bleeding after operation, and the frequency and number of allogeneic transfusions.[6 23 24] Simple elevation of the surgical site may reduce blood loss, but may risk embolism in regions with non-collapsing veins.[25] Obstruction of venous return may increase blood loss and reduction of arterial pressure may cause critical perfusion in the affected region. Topical application of cold devices for tran-

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sient vasoconstriction has been advocated as a means of controlling bleeding for many years. Unfortunately topical cooling (e.g. ice packs, iced saline lavages) has been used without any evidence of efficacy. In contrast with systemic cooling, local cooling causes skin and skeletal muscle vasodilatation which may be counteracted by only a slight increase in vascular resistance, perhaps because of increased blood viscosity.[26] The effect of topical cooling, therefore, may be only transient and cannot be relied on to stop bleeding.

Compared with a conventional surgical approach, adequate endoscopic and similar minimally invasive procedures may reduce bleeding. Argon beam coagulation is better than conventional electrocautery, especially in endoscopic surgery. It is a fast, non-touch technique and improves visibility by not producing smoke.[27,28] Other surgical approaches include local vasoconstriction with epinephrine or related amines, vascular isolation, use of a water jet dissector, microwave tissue coagulation, laser techniques, topical haemostatic agents or the use of tourniquets.[29–31] The use of arterial tourniquets significantly reduced intraoperative blood loss in patients undergoing total knee arthroplasty, but not the rate of allogeneic transfusion, and even after limited tourniquet time, ischaemic damage was found.[32,33] Hence the routine use of a tourniquet is called into question. Tourniquets should not be used in patients with sickle cell anaemia, because local acidosis may induce sickling. Vacuum drains are used routinely to evacuate blood from the surgical field to avoid haematomas. Compared with low vacuum drains, high vacuum drains evacuate more blood initially, but may also cause more damage to tissues, especially if they are in place for more than 24 h. Furthermore, they do not alter the decrease in haemoglobin after operation, number of blood transfusions or wound complications in patients undergoing hip replacement.[34]

Topical agents or the use of impregnated prostheses cannot correct for poor surgical technique and do not necessarily reduce blood loss, but may help to stop bleeding at suture lines, especially in low pressure areas when conventional methods of haemostasis are ineffective.[35–41] Recently, fibrin glue has become the most important of these topical agents, not only to control bleeding but also to repair underlying defects. For example, in trauma patients, fibrin glue is 90–100% effective in controlling haemorrhage from the liver and spleen, whereby splenectomy can be avoided in approximately 80% of cases.[42–44] Although fibrin glue is often considered less effective in high pressure bleeding, it has been used successfully instead of sutures to correct acute aortic insufficiency associated with type A aortic insufficiency.[45] Another preparation, GRF (gelatine–resorcinol–formaline) glue, has also proved to be extremely useful during initial emergency surgery for acute type A aortic dissection.[46]

However, biological topical agents may involve the risk of transmission of diseases and immunological complications. After repeated exposure to bovine thrombin used with fibrin glue, inhibitors of bovine thrombin and/or factor V were found in children and adults causing life threatening bleeding abnormalities.[47–49] Human, and especially human autologous, fibrin glue may avoid these problems.[50]

Blood coagulation

Careful control of blood coagulation is important in the reduction of blood loss, keeping a balance between abnormal bleeding and thrombosis. Before operation, existing coagulopathies may be detected by a thorough history and physical examination. Routine preoperative coagulation screening is capable of detecting only a minority of rare patients with occult bleeding abnormalities and increases unnecessary tests and costs in the remaining patients. A greater number of preoperative patients receive anticoagulant and antiplatelet drugs for various reasons. In cardiac surgery, preoperative treatment with heparin and also with warfarin was not associated with either increased blood loss or transfusion of haemostatic blood products.[23,51,52] In patients with unstable angina, the combination of aspirin and low molecular weight heparin (LMWH) is currently the treatment of choice. Bleeding complications with LMWH were comparable with those with unfractionated heparin and were found primarily in patients undergoing CABG surgery.[53] Non-steroidal anti-inflammatory drugs and aspirin are associated with a slight increase in intra- and postoperative bleeding (e.g. approximately 300 ml in cardiac surgery), which need not necessarily result in increased exposure to allogeneic blood.[54,55] Aspirin should be discontinued only if the patient is particularly sensitive to it (bleeding time>10 min) or if high-risk surgery is anticipated.[56] In patients in whom aspirin is continued, additional treatment with aprotinin or desmopressin reduces bleeding.[57,58] Stopping aspirin may cause abnormally high platelet activity with increased risk of arterial thrombosis, but on the other hand, approximately 40% of patients may fall into the category of non-responders without changes in coagulation.[59,60]

LMWH has become standard care for the prevention of thrombosis. Compared with unfractionated heparin it is at least as effective in general surgery and more effective in orthopaedic surgery. However, the expected reduction of blood loss with LMWH, consequent on less inhibition of platelet function, less effect on the interaction between platelets and endothelium, and no increase in vascular permeability, compared with low dose unfractionated heparin, is not proved, possibly because of different preparations, dosage regimens and differences in study design. Less wound haematomas were found with LMWH in general surgery compared with unfractionated heparin and the amount of blood loss was comparable with placebo in hip surgery, but after major trauma five of six patients with major bleeding had received LMWH.[61–63] The limitations of unfractionated heparin, such as the risk of thrombocytopenia and a significant number of thrombotic events, have stimulated the development of new antithrombotic agents. In a recent European multicentre study of thromboembolic prophylaxis, recombinant hirudin was more effective than LMWH, and there was comparable blood loss in patients after hip surgery.[64]

During operation, desmopressin and both natural (aprotinin) and synthetic antifibrinolytic compounds (tranexamic acid and E amino capric acid) were used to reduce blood loss.[58,65,66] A recent meta-analysis of randomized studies in cardiac surgery found that aprotinin was most effective in reducing the proportion of patients receiving allogeneic transfusions, and of those requiring re-sternotomy because of bleeding. Desmopressin is probably only effective in patients treated previously with aspirin.[57] A high dose aprotinin regimen was significantly more effective than a low dose regimen in attenuating fibrinolysis, reducing bleeding tendency and reducing allogeneic blood requirements.[67] Aprotinin has also been used to control fibrinolysis during orthotopic liver transplantation and in bilateral hip surgery.[68–71]

The importance of the side effects of these drugs is not yet clear. There is a trend to an increase in perioperative infarction and some evidence of higher occlusion rates of distal anastomoses after aprotinin.[72] In addition, aprotinin impairs renal function by overloading tubular reabsorption mechanisms. In a significant number of patients with diabetes, dose-dependent renal dysfunction occurred.[73] Patients with normal preoperative renal function, however, can compensate for both renal dysfunction caused by extracorporeal circulation and additional tubular damage as a result of aprotinin.[74] As aprotinin is a polypeptide, it can cause anaphylactic reactions. During re-exposure, seven of 240 patients suffered mild to severe anaphylactic reactions, but fatal reactions have also been reported.[75 76]

Hypothermia can result from environmental exposure, transfusion of cold fluids or blood products, multiple trauma or as a consequence of therapeutic measures such as hypothermic cardiopulmonary bypass. Hypothermic patients frequently have coagulation abnormalities as hypothermia affects each of the three major components of the clotting process: vessels, platelets and clotting factors.

Platelet function is altered even with mild hypothermia. A decrease in body temperature to values less than 18–26°C is associated with a more marked decrease in peripheral platelet count. In animals, the portal circulation is the primary site of platelet sequestration and up to 80% of platelets return to the circulation on re-warming.[77] Disturbed platelet function may result from cold-induced slowing of the reaction rate of the enzyme thromboxane synthetase, which results in a decrease in thromboxane A_2 production.[78 79] During extracorporeal circulation, the decrease in platelet aggregation was significantly greater in hypothermic than in normothermic patients. After extracorporeal circulation, platelet aggregation recovered incompletely after hypothermia, whereas in normothermic patients it slightly exceeded baseline values. In addition, signs of more extensive endothelial damage or activation were found after hypothermic circulation.[80]

During hypothermia, plasma coagulation is disturbed mainly by enzymatic dysfunction rather than by altered clotting factor levels. In clinical practice, coagulation samples are re-warmed and coagulation tests are standardized to 37°C. Thus standard coagulation tests provide only quantitative information on clotting factor depletion and cannot account for any potential effects of hypothermia on clotting factor function. Clotting tests in hypothermia revealed a significant prolongation of clot formation, which was equivalent to that seen in normothermic patients with significant clotting factor deficits. Slowing of more global tests, such as partial thromboplastin time and prothrombin time, was more pronounced than slowing of a single enzymatic pathway such as thrombin time.[81] This is probably a result of a cumulative effect on different enzymatic processes in the coagulation cascade. Clotting factor deficit is common in hypothermic and seriously injured patients and may potentate the coagulation problem. Disseminated intravascular coagulation found in both neonates and adults after re-warming has several likely causes, such as tissue damage, hypotension and hypoxia.[82]

In patients with primary hip replacement, significantly more blood loss was found and more allogeneic blood was transfused in those who were slightly hypothermic compared with normothermic patients.[83] The aim in the treatment of hypothermic coagulation disorders and platelet dysfunction should be to rewarm to normothermia before transfusion of allogeneic blood products or, if possible, to avoid hypothermia using warming devices.

Conclusion

Measures to reduce surgical blood loss should be made in close co-operation with the staff involved, adjusted to the patient's needs and type of surgery. They should be checked regularly for efficacy and be part of an overall plan that incorporates careful surgery, optimizing coagulation status, obtaining and saving autologous blood, recognition and tolerance of the lowest acceptable packed cell volume in an individual patient, and allogeneic transfusions when physiologically necessary. Using such an approach, Helm and colleagues not only performed 100 consecutive CABG procedures without allogeneic transfusions, but also had less blood loss and greater packed cell volume values both during and after operation.[84]

Blood loss is an inevitable consequence of surgery. However, large differences in the amount of perioperative blood loss between surgeons and institutions lead to the conclusion that there is limited awareness of the risks of anaemia and that strategies to reduce blood loss are not used frequently. In the future, quality assurance programmes will mean that acceptable blood loss and transfusion requirements will be established for standard procedures to reduce the risks of anaemia and also the risks of allogeneic transfusions.

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Controversies in autologous blood procurement

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Numerous professional organizations and federal agencies have endorsed autologous blood transfusion. However, recent advances in blood safety and the additional costs of autologous transfusion have resulted in the reassessment of autologous blood procurement strategies. Current controversy about these strategies in relation to surgery is discussed.

Compensatory erythropoiesis during "standard" autologous donation

A recent retrospective report studied patients who predonated autologous blood before elective hysterectomy.[1] In this study, the only variable known before admission that could predict the need for transfusion was collection of autologous units before operation. The rate of transfusion was 18% in patients who predonated blood compared with 0.8% in those who did not ($P<0.001$). This difference remained significant when corrected for red cell loss during hospital stay and haemoglobin concentration on admission to hospital. Further analysis suggested that patients may have been over transfused with autologous blood, as these patients had a higher haemoglobin concentration at discharge compared with patients transfused with both autologous and allogeneic blood.

As predonation of blood under standard conditions causes anaemia[2 3] and an increased rate of transfusion, some argue that predonation before procedures that are unlikely to have large blood losses may be more harmful to the patient. This suggestion was based on a mathematical model, which predicted that predonation of 2–4 units of blood would decrease both preoperative packed cell volume value (before blood loss) and final packed cell volume value on hospital discharge. For moderate to substantial blood losses (up to 2000 ml), a patient who predonated up to 4 autologous blood units and received blood at a "transfusion trigger" packed cell volume value of 25%, would be discharged with a lower packed cell volume than a patient who did not predonate autologous blood. With no predonation, the patient could sustain blood loss of almost 3000 ml before requiring allogeneic blood transfusion at a packed cell volume value of 25%; predeposit of 2 or 4 units would require autologous blood transfusion after blood loss of 2700 or 2400 ml, respectively. Patients predonating blood would therefore be more likely to be transfused earlier and more frequently than non-donating patients; these predictions were confirmed in the study cited above.[1]

Published studies report great variability in the degree of anaemia induced by predonation of blood. The variation in iatrogenic anaemia is explained in part by heterogenous patient populations and collections occurring close to the surgical date. Some authors have reported a mean decrease in haemoglobin concentration of 1 mg dl^{-1} per unit (i.e. no compensatory erythropoiesis) when blood was donated before hysterectomy,[1] radical prostatectomy[5] or colectomy.[6 7] However, Kasper, Gerlich and Buzello estimated that when 2.7 units were donated over a 3-week interval before cardiac surgery, 1.75 units were "replaced" by compensatory erythropoiesis.[8]

Other studies have found that under "standard, routine" phlebotomy schedules (defined as 1 unit weekly), compensatory erythropoiesis is not as vigorous as noted by Kasper, Gerlich and Buzello (see table 1). Toy, Ahn and Bacchetti[10] reported that only 0.5 of 2 units donated was regenerated over a 20-day interval. Gesemann, Gentner and Scheirmann[11] found comparable erythropoiesis to Kasper, Gerlich and Buzello but only with donation of 4 units over a 4-week interval. One study[12] noted similar rates of compensatory erythropoiesis only when "aggressive" phlebotomy (2 units weekly for 3 weeks) was attempted, and in one series[13] this magnitude of response required i.v. iron therapy. As proposed by Kasper, Gerlich and Buzello,

Table 1 Compensatory red cell (RBC) production during autologous blood collection. Reprinted with permission, from Goodnough and Mercuriali[9]

Reference No.	Units		Interval (weeks)	RBC (ml) production (Mean range)
	Requested	Donated		
8	3	2.7	3	351 (9–719)
10	2	2	3	100
11	4	4	4	390 (64–716) Female 495 (0–766) Male
12	6	4.1	3	549 (499–599) Female 602 (564–640) Male
13	6	2.6	3	328 (250–406) Oral iron
	6	3.3	3	432 (353–511) I v. iron

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early collection of more blood units may be of limited value. One study demonstrated that rapid collection of 3 units over 10 days early in the collection interval resulted in compensatory production of only 1 blood unit (200 ml) over a 4-week interval.[14]

The premise that patients with projected needs of 2 allogeneic blood units should "donate" more autologous blood units[8] seems unwarranted, especially as recent studies have shown that predonation of autologous blood is not only poorly cost-effective but subjects patients to an increased likelihood of transfusion.[15] The result of increased collections would be greater costs, increased discard of untransfused units, and patients made unnecessarily anaemic.

The variability of compensatory erythropoiesis is independent of patient age and sex,[16] but dependent on initial iron status and oral iron supplementation.[17] Even though supplementary iron is normally prescribed during blood donation, iron restricted erythropoiesis has been shown to be a limiting factor to the successful collection of multiple units of blood over a short interval.[18]

The concept that iatrogenic anaemia from predonation of blood may be partially corrected by earlier collection is important as a greater degree of anaemia before operation increases the risk of transfusion, including allogeneic blood.[19–21] Larsen, Foyt and Marengo-Rowe[21] noted that when the last unit of blood was collected at least 15 days before surgery, fewer patients were exposed to allogeneic blood than if blood were collected later. Because normal individuals may take several weeks to regenerate blood lost in donation, and a lower haemoglobin concentration at admission is associated with increased transfusion requirements, it would seem prudent to maximize the time between the last donation and date of surgery. The optimal timing of collections for predonation of blood is an important area for further study.

Who should donate autologous blood?

Several recommendations for selecting patients suitable for autologous blood donation have been published.[22–24] The American Association of Blood Banks recommends only that patients with evidence of systemic infection or unstable angina be excluded.[25] To correctly identify those patients who should donate blood before operation, investigators proposed the use of a schedule of optimal preoperative collection of autologous blood (SOPCAB),[26 27] similar to the maximum surgical blood order schedule (MSBOS).[28] The latter was designed to determine how many allogeneic blood units should be cross-matched. However, a cross-match is less costly and in contrast with predonation of blood, does not involve patient risks. In addition, the SOPCAB was designed to collect enough blood so that less than 10% of patients undergoing a specific surgical procedure would be transfused with allogeneic blood. For a procedure in which the collection of one additional autologous unit would prevent only slightly more patients from being exposed to allogeneic blood, nearly 90% of such units would be discarded. Not all countries adhere to this "10%" guideline. A recent consensus conference on autologous transfusion stated that patients should only be considered for predonation of blood when there is more than a 50% (rather than 10%) likelihood of transfusion.[29]

Attempts to stratify patients undergoing a given surgical procedure into groups at high and low risk of transfusion based on haemoglobin concentration and other factors have shown some promise. In one study, 80% of patients undergoing orthopaedic procedures who would generally be considered candidates for predonation could have been placed into a low-risk group for transfusion, and predonation would not be indicated.[19] A mathematical model[4] which considers estimated blood loss and preoperative packed cell volume can also stratify patients into groups at low and high risk of transfusion, but these schemes need to be verified prospectively. Recent studies of transfusion outcomes in patients undergoing total knee arthroplasty[19] or radical prostatectomy[30] in which there are low rates of allogeneic blood exposure in the absence of any autologous blood procurement (4% and 8%, respectively), have concluded that predonation of blood is not appropriate in these settings.

Is acute normovolaemic haemodilution effective?

The benefit of haemodilution may be less red cell losses because the blood lost at operation has a lower packed cell volume as a result of haemodilution.[31] Mathematical modelling has suggested that severe haemodilution to preoperative packed cell volume values of less than 20%, accompanied by substantial blood losses, would be required before the red cell volume "saved" by haemodilution became clinically important.[32] A case study analysis of patients who had undergone "minimal" acute normovolaemic haemodilution (representing 15% of patients' blood volume) estimated that only 100 ml of RBC (equivalent of 0.5 unit of blood) are "saved".[33 34] With moderate haemodilution (up to 4 units with a target packed cell volume of 28%), the "savings" become more substantial.[35] To date at least six mathematical models of acute normovolaemic haemodilution have been published.[32 36–40] All concur that the savings are small (≤1 allogeneic blood unit) unless profound haemodilution is accompanied by large blood loss (>2 litre).

Autologous blood: acute haemodilution *vs* predonation

It has been recommended previously that patients undergoing radical prostatectomy predonate 3 units of autologous blood; this reduces the prevalence of allogeneic exposure from 66–70% to 14–16%.[41 42] A recent prospective study of moderate acute normovolaemic haemodilution reported that 21% of patients received allogeneic blood[35]; this is comparable with the allogeneic blood exposure rates in patients with 3 predonated units, and is also similar to the 17–20% allogeneic blood exposure rates in elective orthopaedic surgery patients for whom predonation of blood has become standard.[41–43] Thus acute normovolaemic haemodilution appears as efficacious as predonation for radical prostatectomy as it does for patients undergoing total joint arthroplasty. A recent, retrospective European analysis of acute normovolaemic haemodilution in more than 800 patients concluded that allogeneic blood transfusions were reduced from 1.1±1.9 to 0.4±1.9 units/patient.[44]

Two prospective, randomized studies[45 46] and a case-controlled, retrospective comparison[47] of acute normovolaemic haemodilution compared with preoperative autologous blood donation in patients undergoing radical prostatectomy showed that subsequent allogeneic blood exposure was not different (10–20%) for patients undergoing either technique. Lorentz and colleagues[48] studied patients for joint replacement who were allocated randomly to predonation of blood alone (*n*=16), acute normovolaemic haemodilution alone (*n*=16), intra- and postoperative autologous salvage alone (*n*=16) or a control group (*n*=15) with no autologous blood procurement. Patients in each of these groups receiving allogeneic transfusion were two, one, eight and 10, respectively, indicating that acute normovolaemic haemodilution was equally effective as predonation of blood, and that both were superior to autologous blood salvage alone. Goodnough, Merkel and Monk[49] studied 32 patients undergoing total knee arthroplasty, and found that seven (45%) of 15 acute normovolaemic haemodilution patients received allogeneic blood, compared with four (25%) of 17 patients who predonated blood (P=0.17); only one of 11 acute normovolaemic haemodilution patients had received allogeneic blood, compared with none of 10 patients who predonated blood (P<0.05). White and colleagues[50] studied 48 patients undergoing total hip arthroplasty and found that three of 25 acute normovolaemic haemodilution patients received allogeneic blood, which was similar to three of 23 patients who predonated blood.

The value of acute normovolaemic haemodilution is illustrated in figure 1.[51] An adult with an estimated blood volume of 5 litre and an initial packed cell volume of 45% could undergo surgical blood losses of up to 3000 ml yet maintain a packed cell volume value that would remain ≥25% after operation. This packed cell volume is generally considered safe for patients without known risk factors.[52] In this model, haemodilution from an initial packed cell volume of 45% would still allow up to 3500 ml of surgical blood loss, and the packed cell volume could be maintained ≥28%. Haemodilution can thus protect patients who may have unpredictable and substantial blood loss[53] and also maintain packed cell volume values that minimize risks related to ischaemia.[54] These predictions allow a more judicious and informed decision on which blood conservation techniques should be used for a specific patient.

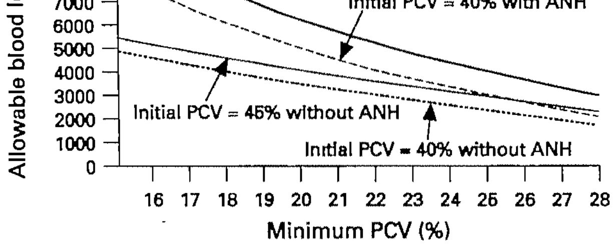

Figure 1 Maximum allowable blood loss in a patient with a blood volume of 5000 ml and an initial packed cell volume value of 45% (solid line) or 40% (broken line), with and without acute normovolaemic haemodilution (ANH). Maximal allowable blood loss in a patient without ANH is calculated by maximum blood loss=EBV×(PCV_0/PCV_F-1, or EBV×ln (PCV_F/PCV_0), where EBV=estimated blood volume, PCV_0=packed cell volume before haemodilution, PCV_F=final target packed cell volume after haemodilution. From Goodnough, Merkel and Monk [51]

Acute normovolaemic haemodilution represents "point of care" autologous blood procurement and has several advantages over predonation of blood. First, autologous blood units procured by acute normovolaemic haemodilution are re-transfused before leaving the operating room and require no inventory or testing costs. Haemodilution also minimizes the possibility of an administrative error that could lead to an ABO-incompatible blood transfusion and death. Predonation of blood does not reduce this risk, which now approximates the mortality from HIV or hepatitis infection from blood transfusion.[55] In addition, blood obtained during acute normovolaemic haemodilution does not require patient time, transport costs or loss of work associated with predonation of blood.

Emerging strategies: "low dose" erythropoietin therapy as an alternative to autologous blood procurement

One approach to enhance the efficacy of haemodilution is to couple this technique with erythropoietin (EPO) therapy. In one study of patients undergoing radical prostatectomy, a three arm trial of moderate haemodilution with EPO therapy (1500 u. kg^{-1} in three divided doses over 3 weeks) was compared with haemodilution alone and also with preoperative autologous donation of 3 units.[49] Four percent of patients treated with EPO and acute normovolaemic haemodilution required allogeneic blood compared with 16% in the two other groups. In EPO-treated patients, mean packed cell volume values were greater than 30% throughout the surgical hospitalization. This benefit may be clinically important, as radical prostatectomy is a procedure that is associated with a 2% risk of perioperative myocardial infarction.[56] Using this approach, the cost of three weekly doses for a 70-kg humans was $1050 (table 2). When the transfusion costs associated with acute haemodilution ($100) are added, the total costs may be estimated as $1100, or approximately twice the cost associated with donation of 3 units of autologous blood.[57] A clinical study of reduced doses of weekly subcutaneous EPO (450 u. kg^{-1}×2 or 300 u. kg^{-1}×2 beginning 14 days before surgery), coupled with haemodilution, has been completed in patients undergoing radical prostatectomy[50]; the use of "low dose" EPO (300 u. kg^{-1}) in this study, together with hamodilution, was equivalent in cost to donation of 3 autologous blood units or transfusion of 2 allogeneic blood units.[62] This conclusion was also reached by Chun[60] in a clinical study of EPO therapy (600 u. kg^{-1}×2) compared with 3 units of predonated blood in patients undergoing radical prostatectomy.

The most cost-effective use of EPO may be to increase packed cell volume values in patients who are anaemic and who are expected to have substantial surgical blood losses.[63] A target preoperative packed cell volume of 45% should minimize the need

Table 2 Costs* of perisurgical EPO therapy. *For a 70-kg patient, at $0.01/unit

Dose	Cost	Reference
1. 300 u. kg^{-1} × 14 days	$2940	Canadian study[57]
2. 600 u. kg^{-1} × 4 weekly	$1680	Goldberg[58]
3. 500 u. kg^{-1} × 5 over 14 days	$1750	Sowade[59]
4. 600 u. kg^{-1} × D-21, D-14 and 300 u. kg^{-1} DOS	$1050	Monk[50]
5. 600 u. kg^{-1} × D-14 and D-7	$820	Chun[60]
6. 300 u. kg^{-1} × D-14 and D-7	$420	Monk[61]

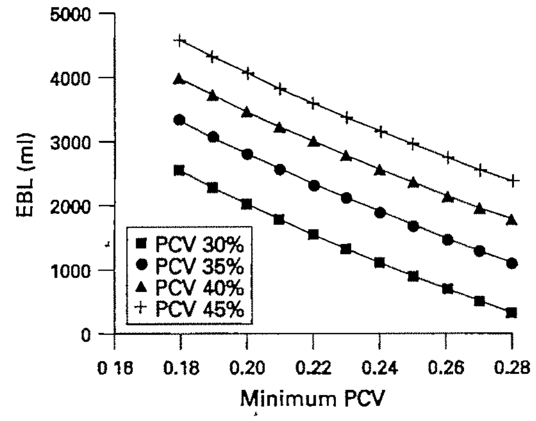

Figure 2 Relationship between estimated blood loss (EBL) and minimum PCV during hospitalization at various initial PCV values (30%, 35%, 40%, 45%) in a surgical patient with a whole blood volume of 5000 ml. Reprinted, with permission, from Cohen and Brecher.[4]

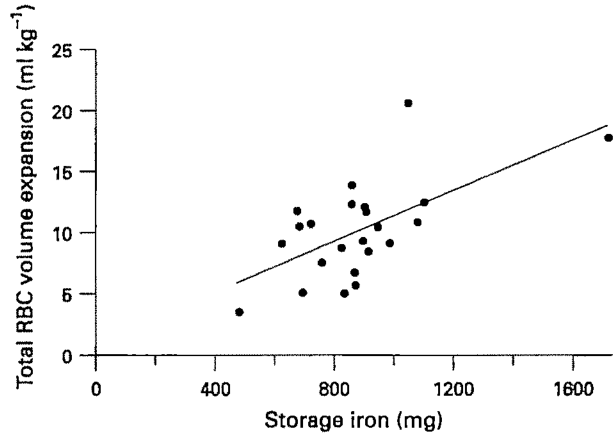

Figure 3 Relationship between initial storage iron (mg) and total red blood cell (RBC) volume expansion in iron-replete EPO-treated patients. Storage iron is derived for each patient based on the initial serum ferritin concentration. Linear regression analysis demonstrated a significant correlation (r=0. 6, P=0. 02). From Goodnough and Marcus.[17]

for allogeneic blood transfusions, especially when accompanied by prudent transfusion practice[64 65] (fig. 2). Patients undergoing more complex surgery with substantial blood loss may require a combination of EPO therapy and autologous blood procurement, such as acute normovolaemic haemodilution. "Low dose" EPO therapy coupled with acute normovolaemic haemodilution may prove equivalent in cost to collection of 3 autologous blood units before elective surgery.

Iron restricted erythropoiesis during blood donation or blood loss

After blood loss, normal individuals have difficulty providing sufficient iron to support rates of erythropoiesis that are greater than three times basal rates.[66] An analysis of the endogenous EPO response to phlebotomy and the effect of EPO therapy on red blood cell production[67] found a good correlation. The maximum marrow response, seen in EPO-treated iron replete patients, was approximately four times basal marrow RBC production.[17] Enhanced plasma iron and transferrin saturation are necessary to produce an even greater marrow response, such as in patients with haemochromatosis,[68] or in patients given i.v. iron.[13] In haemochromatosis, marrow response increases by 6–8-fold over baseline RBC production after aggressive phlebotomy.[68] The term "relative iron deficiency" has been stated by Finch[69] to occur when iron stores are normal but the increased iron requirements exceed the supply of iron.

Iron supplementation with at least 100 mg elemental iron per day taken with food, can provide the increased iron needs in autologous blood donors.[70] For all patients, initial storage iron status does not limit red blood cell production in the presence of oral iron supplementation.[17] However, as illustrated in figure 3, in iron-replete patients there is a significant relationship between storage iron and marrow response in patients receiving erythropoietin therapy. Storage iron is important for maintaining sufficient plasma transferrin saturation for optimal erythropoiesis in the surgical setting.

A recent study of i.v. iron dextran therapy, coupled with EPO therapy, demonstrated rapid erythropoietic responses in patients undergoing surgical repair of hip fracture.[71] However, i.v. iron dextran therapy has side effects that may preclude its routine use in surgical patients. I.v. iron preparations enhance erythropoiesis by giving plasma transferrin saturations rather than with oral ferrous sulphate supplementation. A European trial demonstrated that i.v. iron saccharate and EPO therapy promoted increased erythropoiesis compared with EPO therapy with oral iron supplementation alone.[13] The significant rate of allogeneic blood exposure for both iron-depleted (21%) and iron-replete (18%) patients, despite aggressive autologous blood procurement,[17] emphasizes the value of i.v. iron supplementation in surgical patients.

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Monitoring normovolaemic haemodilution

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Monitoring during normovolaemic haemodilution is undertaken for several reasons. First, monitoring can measure the ability of the patient to cope with anaemia by important physiological adaptations. This type of monitoring includes evaluation of central haemodynamic variables such as central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), heart rate (HR) and arterial pressure, and haemodilutional pathophysiological changes in oxygenation such as shifts to the right of the haemoglobin oxygen dissociation curve (ODC). Another approach to monitoring during haemodilution would be to provide information on the critical level of haemodilution to support decisions regarding perioperative transfusion of red blood cells (RBC). The scientific argument for perioperative RBC transfusion rests on two main assumptions: surgical patients experience adverse outcomes as a result of diminished oxygen-carrying capacity, and RBC transfusions, by enhancing oxygen-carrying capacity, can prevent these adverse outcomes.[1] In other words, tissue oxygenation is the key factor for perioperative RBC transfusions, where possible impairment of tissue oxygenation should be balanced with the risks of transfusions, such as immunomodulation.[2]

In general, oxygen flux into the tissue (Do_2) and finally into the cells, depends on many factors such as arterial oxygen content (haemoglobin, haemoglobin oxygen saturation and physically dissolved oxygen in plasma), systemic haemodynamics (CO), regional blood flow and blood flow properties in the microcirculation, capillary density in the tissue, packed cell volume and erythrocyte transit time in the capillaries, position of the ODC, tissue affinity for oxygen, tissue diffusion coefficient and oxygen transport across the cell membrane.

Regulatory mechanisms by hormones such as catecholamines or by local metabolites in relation to receptors in the macro- and microcirculation play an important role. Haemodilution might interfere with, or change, many of these factors and regulatory mechanisms.

Monitoring systemic haemodynamics

Acute isovolaemic haemodilution induces a decrease in systemic vascular resistance (SVR) almost parallel with a decrease in blood viscosity. Over a wide range of haemoglobin concentrations, the increase in CO compensates for decreased oxygen transport capacity, thereby maintaining Do_2 (the product of CO and arterial oxygen content). Comparing studies in conscious and anaesthetized animals, the increase in CO under anaesthesia in all studies was related closely to the increase in stroke volume (SV), while heart rate (HR) remained constant; in contrast, in conscious experiments an increase in CO was attributable mainly to an increase in HR.[3] Some studies reported an increase in HR during haemodilution under anaesthesia. In all of these studies, however, CVP or PCWP was artificially maintained at baseline values as an indicator of normovolaemia.[4 5] The central haemodynamic variables, such as CVP, PCWP or left ventricle end-diastolic pressure (LVEDP), increased at haemodilution because of increased venous return.[6–8] In a randomized, controlled, clinical study, we found a linear relationship between haemoglobin concentration and measured PCWP. At baseline (haemoglobin 12.1 g dl^{-1}) PCWP was +8 mm Hg while at a haemoglobin of 6.9 g dl^{-1}, PCWP increased to +16 mm Hg.

At the end of surgery and in the first 2 h after operation, the increase in haemoglobin (10.3 g dl^{-1}) with transfusion of blood was associated with a decrease in PCWP to +9 mm Hg despite acute volume loading. In the control group no changes in these variables were observed.[9] The reduction in packed cell volume observed in this study produced a decrease in whole blood viscosity resulting in acceleration of blood flow, especially in low flow vessels with low shear rates in the venous circulation. Increased flow increases venous return and therefore the filling pressures of the heart. It has been postulated that PCWP during normovolaemia is dependent on packed cell volume and that during normovolaemic haemodilution higher CVP or PCWP values should be pursued.[7 9 10]

Monitoring blood flow to organs

Monitoring systemic (total body) variables leaves open concerns about the organ specific variables of flow and oxygenation. A key issue for the use of extreme haemodilution clinically is to find organ specific monitoring that enables the technique to be used safely.[10] In general, in the face of a reduction in Do_2, to meet varying metabolic demands of different

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organs, regional redistribution of blood away from lower extracting beds towards more critical tissues might occur. There are few studies on the distribution of CO during normoxic normovolaemic haemodilution, and most used electromagnetic flow probes which limits the number of organs that can be studied and does not allow assessment of distribution of flow within an organ. Four studies used the radioactive microsphere technique to determine regional perfusion.[6,11–13] All of these studies indicated that redistribution of CO and therefore oxygen transport occurred in favour of vital organs such as the heart and brain. In one study, the pig was selected as the animal model.[6] The cardiovascular system and metabolism of pigs and humans show similarities with respect to size and distribution of coronary vessels, arterial pressure, HR, cardiac index, regional distribution of CO and maximum oxygen consumption.[14–16] In this pig study, during extreme haemodilution (packed cell volume ranged from 28% to 9%) flows increased in all organs, except from the spleen, adrenal gland, hepatic artery flow and skin, with the largest increase in heart (42%) and brain (170%). Circulating catecholamines were excluded as a regulatory mechanism of haemodynamics and regional flow patterns.[6]

These experiments showed that increased flows to several organs were essential compensation for the decrease in arterial oxygen content. Monitoring flows to the brain and heart might be essential during profound haemodilution, especially in patients with compromised blood supply to these organs. Transcranial Doppler ultrasonography can measure middle cerebral artery flow velocity (*v*mca) continuously and non-invasively. Although *v*mca does not reflect absolute cerebral blood flow (CBF), changes in *v*mca are usually directly proportional to changes in CBF.[17,18]

To our knowledge there are no data on the use of transcranial Doppler sonography as a monitoring device during haemodilution, but the device has been used to monitor the effects of several anaesthetics on CBF and cerebrovascular autoregulation.[18–21]

It is also possible to measure flow to the heart in patients using a coronary sinus thermodilution catheter. Coronary sinus blood flow can be measured accurately by continuous thermodilution.[22,23] As with transcranial Doppler ultrasonography, to our knowledge there are no data on the use of this technique during haemodilution. The technique has been used in humans to evaluate coronary flow adaptations in response to increased cardiac oxygen demand,[24] but is highly invasive, needs an experienced operator and is therefore not used in routine monitoring.

Monitoring systemic oxygenation

With a decline in haemoglobin concentration, the total arterial oxygen content of the blood decreases. As discussed above, the increase in CO over a wide range of haemoglobin concentrations compensates for a decreased oxygen transport capacity, thereby maintaining Do_2 until the compensatory increase in CO is exhausted. Any further decrease in arterial oxygen content leads to an increased extraction ratio (ER=$\dot{V}o_2/Do_2$) up to a maximum, dependent on the position of the ODC[3] and oxygen demand. A further reduction in haemoglobin concentration produces oxygen supply dependency of $\dot{V}o_2$. During haemodilution ER might vary not only as a result of changes in Do_2 but also because of changes in $\dot{V}o_2$. In some reports increases in $\dot{V}o_2$ at the initial stages of stepwise-induced normovolaemic haemodilution have been found.[6,25,26] It has been suggested that with increased CO extra oxygen is used by the heart and this alone could account for this increase in $\dot{V}o_2$.

On the other hand, induction of anaesthesia in patients decreases $\dot{V}o_2$ by 10%, while $\dot{V}o_2$ in the first hours after anaesthesia increases by 20% compared with pre-anaesthetic values.[27] Therefore, during surgery and anaesthesia a more pronounced haemodilution might be more acceptable than during the initial postoperative phase.

For monitoring systemic oxygenation, global variables of tissue oxygenation and variables of the balance between oxygen need and oxygen flux should be available. During major surgery with a pulmonary artery thermodilution catheter inserted, CO and analysis of arterial and mixed venous blood can be undertaken. From these values, $Do2$, $\dot{V}o_2$ and ER can be calculated. Furthermore, continuous monitoring of $S\bar{v}_{o_2}$ has been developed and is used for measurement of oxygen transport patterns.[28–30] The accuracy of such fibreoptic devices is not affected by acute changes in packed cell volume or CO and they are useful during haemodilution.[31,32] $S\bar{v}_{o_2}$ was found to correlate well with ER during haemodilution and therefore reflects the overall balance between Do_2 and $\dot{V}o_2$.[33,34]

In pigs, at the critical point of haemodilution ($\dot{V}o_2$ became dependent on Do_2) $S\bar{v}_{o_2}$ was 44.2±7.9%,[34] while in a case report on haemodilution in humans, a critical value of 56% was found.[35] The critical point of $S\bar{v}_{o_2}$ or ER during haemodilution is related to the position of the ODC. In pig experiments a direct, significant, linear relationship was observed between the shift to the right of ODC and the increase in ER (and $S\bar{v}_{o_2}$ also) during Do_2 supply dependency of $\dot{V}o_2$.[36] Therefore, continuous $S\bar{v}_{o_2}$ measurements are useful during haemodilution to monitor changes in oxygen balance but cannot be used as an absolute indicator of hypoxia. Mixed venous Po_2 ($P\bar{v}_{o_2}$) however, might be more sensitive to changes in several factors influencing oxygenation, especially when changes in ODC are involved.[37,38] $P\bar{v}_{o_2}$ is thought to reflect overall Po_2 in the microvasculature as the driving pressure for oxygen diffusion into the tissue. Some authors reported that under some conditions such as severe shock, microcirculatory Po_2 ($P\text{mic}_{o_2}$) can become lower then venous Po_2.[39,40] Also in pigs, we showed that during haemorrhagic shock, $P\text{mic}_{o_2}$ decreased to values lower than venous Po_2 (unpublished data), but changes in $P\bar{v}_{o_2}$ parallelled $P\text{mic}_{o_2}$. Therefore, venous Po_2 is not the same as end-capillary Po_2 but changes in $P\bar{v}_{o_2}$ reflect changes in overall $P\text{mic}_{o_2}$. In several animal experiments and clinical situations, except septic shock, a critical $P\bar{v}_{o_2}$ of 30–33 mm Hg has been found.[34,35,41,42] In pigs, at the critical point of haemodilution, a $P\bar{v}_{o_2}$ of 32.3±3.1 mm Hg was found[34] while in a case report on haemodilution in a human, the critical $P\bar{v}_{o_2}$ was 34 mm Hg.[35]

The position of the ODC influences the maximum ER before Do_2 supply dependency of $\dot{V}o_2$ starts.

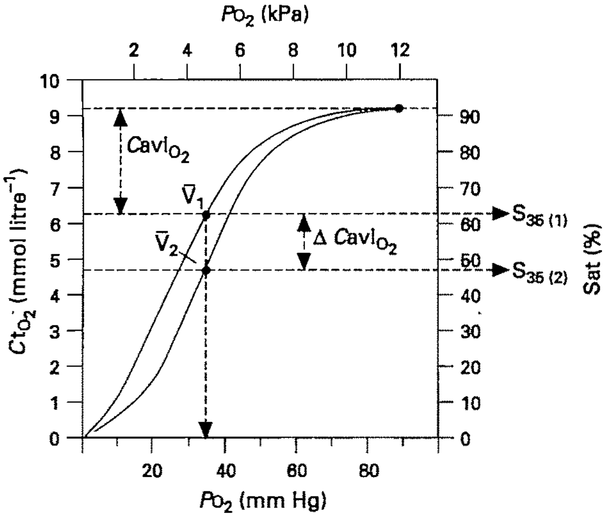

Figure 1 Effect of changes in oxygen dissociation curve (ODC) on S_{35} (saturation of haemoglobin at Po_2=35 mm Hg), and the available oxygen content ($Cavl_{O_2}$). $\bar{V}_1$ indicates the intersection with the critical venous Po_2; $\bar{V}_2$=after shift to the right of the ODC.

Acute shifts to the right of coronary sinus, venous and arterial blood have been reported during signs of hypoxia of the heart in humans.[43–45] Chronically reduced haemoglobin concentration is compensated for by improved oxygen unloading, afforded by the increased P50.[46 47] In dogs, an acute change in ODC during acute haemodilution occurred but not before packed cell volume decreased to less than 10%.[48]

In pigs with acute haemodilution, the ODC shifts to the right (for pH-corrected) related to changes in $P\bar{v}_{O_2}$, in common with the acute changes in P50 during signs of hypoxia of the heart.[36] Also, in the human, P50 changed when the critical $P\bar{v}_{O_2}$ was reached.[35]

A concept in monitoring systemic oxygenation that includes the effect of changes in ODC has been introduced using the S_{35} (saturation of haemoglobin at Po_2=35 mm Hg).[36] Real arterial available oxygen content ($Cavl_{O_2}$) can be calculated from a single blood-gas analysis as the maximum amount of oxygen that can be extracted from haemoglobin in several organs before oxygen diffusion into tissue becomes compromised and $\dot{V}o_2$ decreases (fig. 1). The relationship between arteriovenous oxygen content difference and $Cavl_{O_2}$ (Erav) gives a realistic index of the available oxygen supply and $\dot{V}o_2$, including the effect of changes in ODC. Comparing haemodilution in pig experiments with a fatal human case revealed differences in critical ER (0.57 *vs* 0.46) but not in critical Erav (both 1.0).

During hypoxia, lactic acidosis may occur. Currently, the lactate concentration in blood can be measured within minutes and can be used as a global variable of tissue hypoxia. In one study of extreme haemodilution, although haemoglobin concentration decreased to 3.0 g dl^{-1}, none of the patients' serum lactate concentrations were outside the normal range.[7]

Monitoring oxygenation of organs

It can be argued that global variables of oxygenation may not reflect tissue oxygenation of single organs at risk. In this respect, most attention has been paid to the vital organs such as the heart and brain. However, studying the redistribution of flows during extreme haemodilution, concern has been directed at the splanchnic area, as although Do_2 to most organs remained constant, it decreased to the splanchnic organs.[6] At present, only one technique is in clinical use for monitoring the metabolism of the splanchnic area. Mucosal pH of the gut (pHi) or sigmoid colon can be determined with tonometry.[49] In a study of patients undergoing major surgery, pHi <7.32 at the end of surgery was associated with more major complications and greater mortality in the postoperative period.[50] In patients undergoing surgery of the abdominal aorta, a gastric pHi of 7.20 and a sigmoid pHi of 7.10 were found to be critical.[51] So far tonometry has not been used as a monitoring tool in transfusion practice.

It has been postulated that during haemodilution, CO increases without an increase in myocardial contractility and therefore without increased oxygen consumption. The current evidence shows that with haemodilution in animals and in humans the oxygen demand of the heart is increased.[6] In pigs with changing packed cell volume from 28% to 9% the oxygen consumption of the left ventricle increased by 105%. Fortunately, this increase in consumption was met by an increased oxygen availability, because flows to the heart increased by 420%. However, during more profound haemodilution, ischaemia of the myocardium may occur, especially in patients with coronary artery disease. Therefore, in some patients it is important to monitor myocardial function.

With a coronary sinus thermodilution catheter *in situ* it is possible to measure oxygen flux to the heart, myocardial oxygen consumption and the balance between these two variables, but the technique is too complicated for routine use. It is questionable whether standard single-lead or three-lead electrocardiogram with continuous ST-segment analysis or CO as a variable are sensitive enough to detect early signs of myocardial hypoxia. The answer is probably no. Continuous transoesophageal echocardiography can be used to evaluate patterns of pathological movement in various regions of the left ventricle and could at an early stage be taken as an indicator of oxygen depletion.

Similarly, in the brain during normovolaemic haemodilution, decreased oxygen transport capacity is compensated for by an increase in flow, out of proportion to the increase in CO. Oxygen flux to the brain remained constant until a packed cell volume of 12% and decreased slightly with further reduction of arterial oxygen content.[6] Use of a jugular bulb catheter enables information to be obtained on the oxygenation of the brain. Jugular bulb catheters are simple, safe and practical for both intermittent and continuous monitoring of jugular venous bulb oxygen saturation and blood-gas analysis. Measurement of jugular bulb blood oxygen content allows calculation of the arteriovenous oxygen content difference ($AVDO_2$) and therefore the oxygen extraction ratio for the brain.[52 53] Using transcranial Doppler ultrasonography and jugular bulb oximetry, a reasonable estimate of the ratio between flow and oxygenation of the brain can be obtained.

Monitoring the microcirculation and tissues

In a capillary where the vessel diameter approximates to the red blood cell diameter, a clear distinction must be made between the red blood cell volume within the capillary (tube packed cell volume) and the red cell volume flowing through the capillary at an instant in time. Under physiological conditions, the tube packed cell volume is very heterogeneous inside the capillary bed and can be up to six times lower than systemic packed cell volume.[54–56] Isovolaemic haemodilution exerts some distinct effects on the microcirculation. During moderate haemodilution, with a systemic packed cell volume of approximately 30%, red blood cell flux through the microvasculature increases. During further haemodilution to systemic packed cell volume values less than 20%, redistribution of red blood cells and plasma through the microcirculatory network occurs, the density of perfused capillaries increases, and flow and packed cell volume values become more homogeneous.[56 57] In general, it can be assumed that a decrease in systemic packed cell volume to values of approximately 50% of normal values does not affect capillary packed cell volume.[55 58] Changing systemic packed cell volume does not result in directly proportional changes in capillary cell content or red cell flow distribution into the tissue.

Nevertheless, monitoring of the microcirculation might be of great importance during haemodilution. Recently, reflectance videophotometry has been developed by which the microcirculation in any part of the human body can be seen non-invasively. This monitoring device may become important when the pictures can be quantified, not only for understanding changes in the microcirculation but also as a warning device for deterioration of the microcirculation during surgery and haemodilution in different organs such as the splanchnic area.

To assess tissue oxygenation it would be very helpful to measure $P\mathrm{o}_2$ and haemoglobin saturation inside the capillary network and to relate these values to local venous $P\mathrm{o}_2$ values. The development of optical spectroscopy has introduced these possibilities in experimental models. Absorption spectroscopy has been used successfully in the evaluation of the distribution of haemoglobin saturation in the capillary network.[59] The introduction of Pd-porphyrin phosphorescent dyes allowed *in vivo* measurements of microvascular $P\mathrm{o}_2$.[60 61] In the near future, these techniques in experimental models may elicit the relationship between microvascular $P\mathrm{o}_2$ (driving pressure for diffusion of oxygen into the tissue), venous $P\mathrm{o}_2$ and $P\bar{\mathrm{v}}_{\mathrm{O}_2}$ during normovolaemic haemodilution. To obtain an even better picture of tissue oxygenation, measurements inside the tissue itself should be appropriate. For example, insertion of a microdialysis catheter into organs at risk has been suggested.[10] With this technique it is possible to measure online, in the tissue, several metabolites, including lactate. A tubular dialysis membrane is introduced into the tissue or placed in contact with a moist surface. The small tube is perfused continuously with a liquid (1–6 μl min^{-1}) that equilibrates with the fluid outside the tube by diffusion in both directions.[62 63] The application of the technique may be time consuming because of calibration procedures.

NADH fluorescence can be used in experimental models to monitor cellular metabolism, because NADH fluoresces when excited at 365 nm while NAD$^+$ does not.[64] This application of fluorescence has been used to measure the energy state of hearts. Also, with near infrared spectroscopy intracellular metabolism can be studied.[65]

Haemoglobin concentration as transfusion trigger

In clinical situations, despite several routine possibilities for monitoring oxygenation, physicians' decisions to transfuse are mostly based on haemoglobin measurements. For this reason it is important to know at which haemoglobin concentration systemic oxygenation might become critical. As discussed before, a $P\bar{\mathrm{v}}_{\mathrm{O}_2}$ of 33 mm Hg has been found at the critical point of haemodilution. Using several keywords, a search of the literature has been performed to find the relationship between haemoglobin concentration and $P\bar{\mathrm{v}}_{\mathrm{O}_2}$ values in human during haemodilution and anaesthesia. Of 124 publications, five studies[8 9 66–68] involving 102 patients were suitable for analysis. From these 102 patients, 18 patients underwent haemodilution to such a degree that they reached a $P\bar{\mathrm{v}}_{\mathrm{O}_2}$ value of 33 mm Hg. Haemoglobin concentration at this point of haemodilution was 7.2±0.3 g dl^{-1}. Furthermore, we searched the literature for Jehovah's Witness patients with severe anaemia; 25 patients with haemoglobin concentrations ranging from 1.4 to 4.6 g dl^{-1} were found of whom 20 patients survived and five died. At haemoglobin concentrations less than 2.4 g dl^{-1}, mortality rate was 50%, while mortality rate was 6% when haemoglobin concentration exceeded 2.4 g dl^{-1}. However, a publication bias might have influenced these values as survivors are reported more often than patients who die. Other workers reviewed the literature on the treatment of Jehovah's Witnesses, including 4722 patients. They found that anaemia-related mortality started at a haemoglobin concentration of 5.0 g dl^{-1} or less.[69]

There are no prospective, randomized, clinical studies on blood transfusion in the postoperative period and therefore no evidence-based transfusion trigger for the surgical patient. A study in 43 European hospitals on safe and good use of blood in surgery (Sanguis project) showed that after operation, patients (n=4501, table 1) were transfused at a packed cell volume of 27±3% (haemoglobin 8.6 ±1.0 g dl^{-1}).[70]

Conclusion

There are many possibilities for monitoring oxygenation during haemodilution, more than are generally realized (table 2). Some are only applicable in animal models but many can be used in humans.

For any individual patient, the physician can choose modalities depending on the type of surgery,

Table 1 Postoperative packed cell volume (PCV) values at the start of transfusions (from the Sanguis project[70])

Procedure	*n*	PCV
Right and left hemicolectomy	995	28±3.7
Coronary artery grafting	1166	28±2 9
Abdominal aortic aneurysmectomy	693	27±2.5
Total hip replacement	1647	26±3 0
Total	4501	27±3.0

Table 2 Monitoring during haemodilution, invasive (i) and non-invasive (n).

	i/n	In humans
CVP catheter	i	+
Pulmonary artery catheter (systemic haemodynamics, Do_2, $\dot{V}o_2$)	i	+
Transcranial Doppler ultrasonography	n	+
Coronary sinus thermodilution	i	+
Mixed venous oximetry ($P\bar{v}_{o_2}$)	i	+
Mofidied extraction ratio (ERav)	i	+
Closed circuit Vo_2 measurements	n	+
Systemic lactate measurements	i	+
Tonometry (gut, sigmoid)	n	+
Continuous ST-analysis	n	+
Jugular bulb catheter, oximetry	i	+
Reflectance videophotometry (microcirculation)	n	+
Echocardiography	n	+
Pd-porphyrin phosphorescence ($Pmic_{o_2}$)	i	–
Microdialysis	i	+
NADH fluorescence	i	+
Near infrared spectroscopy	n	+

expected blood loss and general condition of the patient. The risks involved with some types of invasive monitoring have to be balanced with the long-term hazards of blood transfusion.

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Hyperoxaemia in extreme haemodilution

O. HABLER AND K. MEßMER

Acute normovolaemic haemodilution

Acute normovolaemic haemodilution is the simultaneous exchange of whole blood with an identical volume of an iso-oncotic colloid (e.g. 6% hydroxyethyl starch, 6% dextran, etc.) or three times the volume of an isotonic crystalloid (e.g. Ringer's lactate). The resulting dilutional anaemia is compensated for by an increase in cardiac output and enhanced arterial oxygen extraction. When blood volume is kept constant (essential during acute normovolaemic haemodilution) large amounts of autologous blood may be collected without jeopardizing tissue oxygenation. The physiological limit of dilutional anaemia is however reached when oxygen consumption ($\dot{V}o_2$) becomes dependent on oxygen delivery (Do_2). At that point, a decrease in $\dot{V}o_2$ suggests the onset of tissue hypoxia and the packed cell volume corresponding to this state is called the "critical" packed cell volume for tissue oxygenation (PCV_{crit}). When performing acute normovolaemic haemodilution in healthy subjects, using conventional colloids or crystalloids for dilution, PCV_{crit} is in the range 7–13%[1,2] depending on the type of anaesthesia, inspiratory oxygen fraction ($F\text{I}_{\text{O}_2}$) and body temperature.

In patients undergoing elective surgery, acute normovolaemic haemodilution is a simple means of obtaining fresh whole blood, containing coagulation factors and platelets, immediately before surgery. As acute normovolaemic haemodilution has been shown to reduce the need for allogeneic transfusion in elective surgery,[3] and to be more cost-effective than preoperative autologous donation,[3,4] it has become an important part of methods to save blood. In healthy anaesthetized children, haemodilution to haemoglobin concentrations as low as 3 g dl^{-1} can be performed without changes in oxygen consumption.[5] This is an extreme approach to extend the method of acute normovolaemic haemodilution to the limits of oxygen transport physiology; usually haemodilution is not as extreme. To preserve a margin of safety for tissue oxygenation and organ function in patients with intact myocardial function, intentional acute normovolaemic haemodilution should be performed to a target packed cell volume of not lower than 21% (haemoglobin concentration 7 g dl^{-1}). In elderly patients[6] and those with coronary vessel disease,[7] packed cell volume values not lower than 30% are recommended in the perioperative period.

If sudden blood loss occurs in a haemodiluted patient, the arterial oxygen content of blood can be increased by retransfusion of withdrawn autologous acute normovolaemic haemodilution blood. However, autologous blood may be exhausted before definite control of bleeding. Allogeneic transfusion may then be necessary, exposing the patient to transfusion-related risks such as infection, haemolysis and immunosuppression.[8]

Instead of immediate red blood cell transfusion, hyperoxic ventilation ($F\text{I}_{\text{O}_2}$ 1.0) can be used to rapidly increase arterial oxygen content by increasing the amount of physically dissolved oxygen in plasma. Because of the linear relationship between arterial partial pressure of oxygen Pa_{O_2} and arterial oxygen content in plasma, the quantity of dissolved oxygen depends only on arterial Po_2 and plasma volume. As the proportion of plasma is significantly increased in haemodiluted subjects, it can provide more oxygen, especially in the presence of hyperoxaemia.[9]

Effects of hyperoxaemia on acute normovolaemic haemodilution-induced compensatory mechanisms

Hyperoxaemia reduces the compensatory mechanisms that occur with dilutional anaemia.[10,11] We have verified this recently in anaesthetized dogs breathing air and haemodiluted to a target packed cell volume of 21%.[11] As expected, dilutional anaemia induced a significant increase in cardiac index and arterial oxygen extraction. Tissue oxygenation, measured directly by use of a polarographic oxygen-sensitive multiwire electrode on the surface of the liver and skeletal muscle, remained constant (fig. 1).

Subsequent exposure to hyperoxic ventilation ($F\text{I}_{\text{O}_2}$ 1.0, Pa_{O_2} approximately 66.7 kPa) reversed completely the acute normovolaemic haemodilution-induced increase in cardiac index and partially reversed the decrease in systemic vascular resistance (fig. 2). As the increase in arterial oxygen content did not fully compensate for the decrease in cardiac index, oxygen delivery did not change significantly during hyperoxaemia (fig. 3).

Nevertheless, mean tissue Po_2 in both liver (ns) and skeletal muscle ($P<0.05$) increased, suggesting improved tissue oxygenation with hyperoxic ventilation (fig. 1). To assess the effect of hyperoxic ventilation, acute normovolaemic haemodilution was

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Keywords. blood, haemodilution; oxygen, consumption; oxygen, delivery; blood, transfusion

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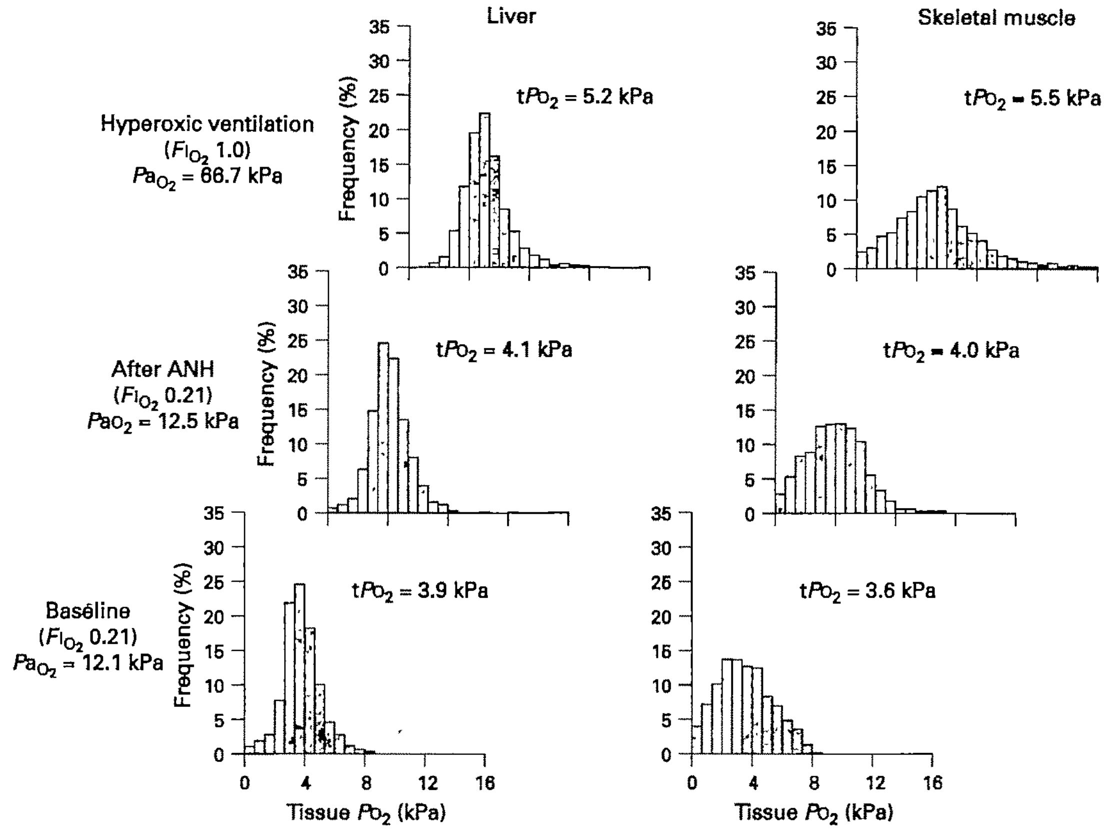

Figure 1 Frequency distribution of tissue PO_2 values measured on the surface of the liver and skeletal muscle with an oxygen sensitive surface electrode (MDO-electrode) in anaesthetized dogs breathing room air (baseline), after acute normovolaemic haemodilution on room air to a packed cell volume of 21% (after ANH) and after increasing FI_{O_2} to 1.0 (hyperoxic ventilation). tPO_2=Mean tissue PO_2. Adapted from Habler and colleagues.[11]

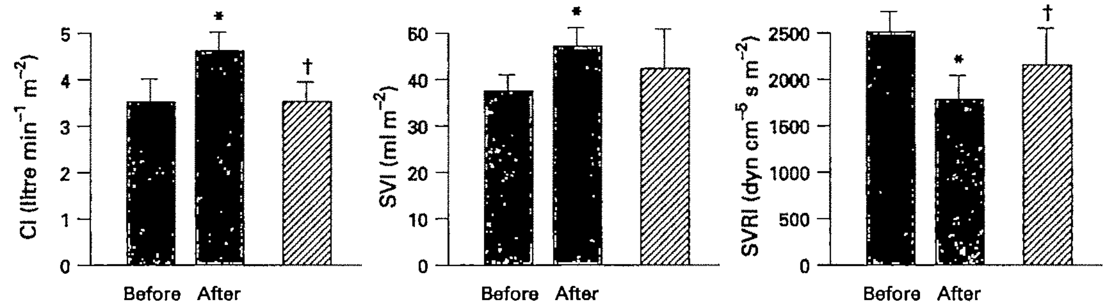

Figure 2 Haemodynamic changes (cardiac index (CI), stroke volume index (SVI) and systemic vascular resistance index (SVRI)) with acute normovolaemic haemodilution (ANH) to a haemoglobin concentration of 7 g dl^{-1} and then with hyperoxic ventilation (FI_{O_2} 1.0).[11] *$P<0.05$, before *vs* after ANH; †$P<0.05$, after ANH *vs* FI_{O_2} 1.0

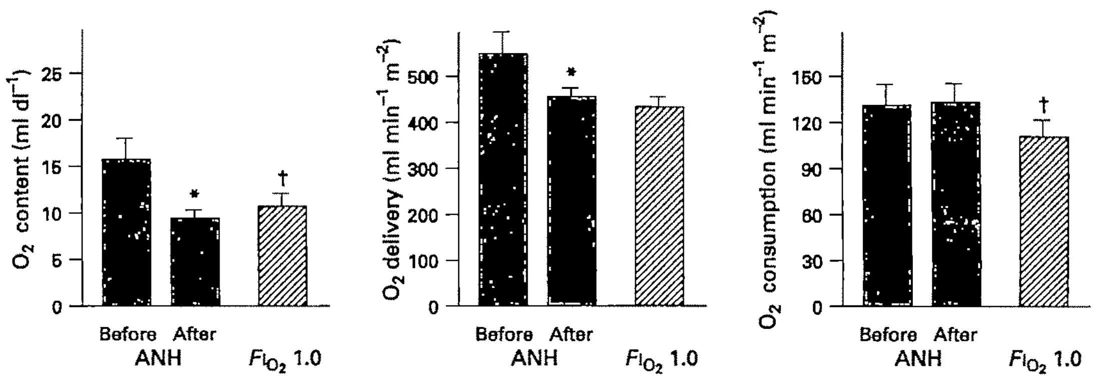

Figure 3 Changes in arterial oxygen content, oxygen delivery and oxygen consumption with acute normovolaemic haemodilution (ANH) to a haemoglobin concentration of 7 g dl^{-1} and then with hyperoxic ventilation (FI_{O_2} 1.0).[11] *$P<0.05$, before *vs* after ANH; †$P<0.05$, after ANH *vs* FI_{O_2} 1.0.

continued until the effects observed with the onset of hyperoxaemia were abolished. This occurred after an additional 19% exchange of blood volume at a mean haemoglobin concentration of 5.8 g dl^{-1}. We calculated that the benefit obtained with hyperoxic ventilation was equivalent to the benefit that would have been expected after transfusion of 11–15 g of haemoglobin. Related to a patient weighing 80 kg, this corresponds to transfusion of approximately 1 unit of packed red blood cells (estimated mean volume 350 ml, mean packed cell volume 60%).

Mechanisms of hyperoxaemia-related haemodynamic effects during acute normovolaemic haemodilution

The effects of hyperoxaemia on acute normovolaemic haemodilution-induced haemodynamic changes include: (1) circulatory adaptation to increased arterial oxygen content; (2) reduction of acute normovolaemic haemodilution-induced sympathetic tone; and/or (3) hyperoxaemia-induced arteriolar vasoconstriction.

Possibility (1), that increased arterial oxygen content might allow for a decrease in haemodynamic compensatory mechanisms during acute normovolaemic haemodilution and hyperoxaemia suggests that these mechanisms are caused by the dilutional decrease in oxygen content. This possibility is controversial. Acute normovolaemic haemodilution in combination with hyperbaric oxygenation,[12] thus maintaining blood oxygen content, causes the same increase in cardiac index as does normobaric haemodilution. In contrast, if oxygen content is reduced without changing blood viscosity (acute normovolaemic haemodilution with methaemoglobin[13] or hyperviscous dextran solution),[14] no increase in cardiac output occurs. Thus it is more likely that the reduction in blood viscosity caused by dilution leads to the observed increase in ventricular stroke volume during acute normovolaemic haemodilution, rather than reduced arterial oxygen content.

While transfusion of red blood cells in haemodiluted subjects reduces ventricular stroke volume by a concomitant increase in blood viscosity, hyperoxaemia influences neither blood viscosity nor ventricular stroke volume, and the observed reduction in cardiac index in these circumstances is caused by a decrease in heart rate.[10 11] In hyperoxaemia, approximately 15% of Do_2 and approximately 50% of $\dot{V}o_2$ are provided by oxygen that is dissolved in plasma[11] (fig. 4). Since plasma oxygen is highly diffusable and therefore preferentially used for tissue oxygenation (prior to the consumption of haemoglobin-bound oxygen), the decrease in cardiac index during hyperoxaemia in haemodiluted subjects may be explained partially by circulatory adaptation to greater oxygen delivery from physically dissolved oxygen.

Possibility (2) suggests that acute normovolaemic haemodilution causes sympathetic activation. At very low packed cell volume values (<15%), compensation for dilutional anaemia by increases in ventricular stroke volume and oxygen extraction become maximal and cardiac output is increased further by onset of tachycardia. Although this effect can be blunted partially by surgical denervation of the heart[15] or by pharmacological block of beta-adrenoreceptors,[16-18] it is not uniformly reproducible. In other studies, bilateral adrenalectomy and additional pharmacological ganglion block[19] and also beta-adrenoreceptor block[10] in dogs haemodiluted to packed cell volume values of 7–15% caused haemodynamic changes comparable with those in control animals. Moreover, increased sympathetic activity after acute normovolaemic haemodilution has not been verified by increased plasma concentrations of catecholamines. Changes in myocardial contractility, a variable that is extremely sensitive to changes in sympathetic stimulation, remained unaltered after the onset of hyperoxaemia in haemodiluted dogs.[11]

The vasoconstrictive effect of hyperoxaemia on microvessels (arterioles, venules) has been described extensively *in vitro* (isolated vessel segments)[20] and *in vivo* (intravital microscopy,[21] laser Doppler flowmetry, etc.).[22] It seems to be mediated locally[23] by products of the arachidonic acid metabolic pathway (e.g. 20-hydroxy-eicosa-tetraenoic acid (20-HETE))[24] and can be blocked completely by indomethacin[25] and cytochrome P-450 inhibitors.[24] Hyperoxaemia increases systemic vascular resistance and decreases cardiac output and oxygen consumption in animals with normal packed cell volume.[26] Therefore, it is likely that the reduction in these variables in dilutional anaemia and hyperoxic ventilation is to a greater extent caused by hyperoxaemic vasoconstriction rather than by the other mechanisms discussed above.

In studies investigating the effects of hyperoxaemia in subjects with normal packed cell volume values, the observed "broadening" and "scattering" of tissue Po_2 histograms and the observation of hypoxic tissue Po_2 values (0–1.3 kPa) has been interpreted as a sign of impaired local oxygen delivery caused by hyper-

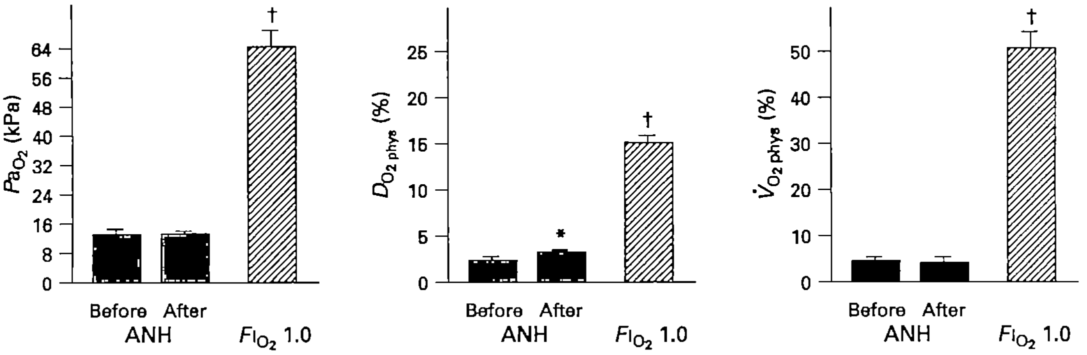

Figure 4 Contribution of oxygen physically dissolved in plasma to oxygen delivery ($Do_{2\,phys}$) and oxygen consumption ($\dot{V}o_{2\,phys}$) caused by acute normovolaemic haemodilution (ANH) to a haemoglobin concentration of 7 g dl^{-1} and then with hyperoxic ventilation (F_{IO_2} 1.0).[11] $*P<0.05$, before *vs* after ANH; $\dagger P<0.05$, after ANH *vs* F_{IO_2} 1.0.

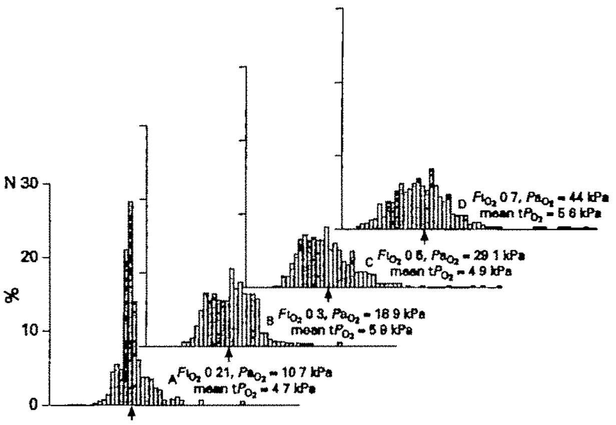

Figure 5 Frequency distribution of tissue Po_2 (tPo_2) values measured on the surface of a skeletal muscle by an oxygen sensitive surface electrode (MDO-electrode) in anaesthetized rabbits ventilated with room air (A), and 30% (B), 50% (C) and 70% (D) oxygen. Adapted from Thorborg, Malmqvist and Lund.[27]

oxic vasoconstriction and abnormal distribution of microvascular blood flow[27] (fig. 5).

Thus hyperoxaemia was considered harmful for tissues perfused with blood with normal PCV. In our experiments in haemodiluted dogs (haemoglobin 7 g dl^{-1}),[11] the Gaussian distribution of single measured tissue Po_2 values was preserved during hyperoxaemia (fig. 2). An increase in hypoxic tissue Po_2 values was not detected and the right shift of the histograms may even be interpreted as improved tissue oxygenation. In addition, non-linear analysis of blood flow distribution did not show any increase in microcirculatory blood flow heterogeneity during hyperoxaemia in haemodiluted subjects.[28 29] This shows that packed cell volume has an important influence on microvascular changes caused by hyperoxaemia. In haemodiluted subjects, the microcirculatory changes caused by hyperoxaemia seem to be absent, as acute normovolaemic haemodilution-induced vasodilatation leads to less marked net changes in arteriolar diameter caused by hyperoxaemia.

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"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL

Recent advances in opioid pharmacology

Opioids produce analgesia but also respiratory depression, dependence and a variety of other troublesome side effects. With this in mind, several alternatives to opioids in the treatment of pain have been suggested and used effectively, as have different ways of using opioids. Despite this, the clinical holy grail of quality analgesia without respiratory depression[1] has yet to be attained.

This issue of the *British Journal of Anaesthesia* results from a meeting held at Leicester University in September 1997 – the Eighth International Symposium of Pain and Anaesthesia – at which several leading authorities gave up-to-date reviews on new developments in opioid pharmacology and speculated on future research. Their talks are the basis of articles in this issue, which also includes topical reviews on the pain/opioid theme and, to keep the issue as current as possible, abstracts associated with the symposium "Recent Advances in Opioid Pharmacology" held on the first day of the meeting. Since September last year there have been important further developments, some of which are noted below.

In the past 5–6 years our understanding of opioid pharmacology has advanced monumentally, as a result of the simultaneous cloning by Evans and colleagues[2] and Kieffer and colleagues[3] of the δ opioid receptor (named DOR). The studies that followed (reviewed in references 4–7) have led many of us to question our understanding and basic beliefs of opioid pharmacology. For example, what of opioid receptor subtypes? We all know that respiration is depressed when large doses of opioid are given to humans. This observation, coupled with the pharmacology of drugs like naloxonazine[8] and the dermorphin analogue TAPS,[9] led to the description of μ1 and μ2 subtypes of μ opioid receptors, with the former mediating analgesia and the latter producing respiratory depression.[4–7] The cloning of the μ opioid receptor (MOR), which followed cloning of the κ receptor (KOR),[4–7] does not lend support to the existence of separate μ1 and μ2 subtypes. Do these receptors result from post-translation modification of a common protein? This remains to be determined. To add to this confusion the existance has been proposed, using antisense oligonucleotide technology, of a morphine-6-glucuronide receptor.[10] Studies of this type were again prompted by publication in 1992 of the DOR sequence by Evans and colleagues[2] and Kieffer and colleagues.[3] So what message can be gleaned from these studies? First, that opioids surely produce analgesia and respiratory depression. Second, that the structural and pharmacological studies do not tie up. Third, we can be sure that morphine acting at the μ receptor produces analgesia, as Brigitte Kieffer's group in Strasbourg have generated a μ knockout mouse (a mouse engineered to lack μ opioid receptors) in which morphine does not produce analgesia.[11] In an attempt to unify opioid receptor classification, the International Union of Pharmacology (IUPHAR) has reclassified opioid receptors as OP$_1$ (δ), OP$_2$ (κ) and OP$_3$ (μ) (table 1).[12]

The μ receptor story took a further interesting turn in 1997 when endomorphins 1 and 2 were described. These peptides display extremely high affinity and selectivity for μ receptors[13] and have recently been identified in human brain.[14] Endomorphins 1 and 2 produce spinal[15] and supraspinal[13] analgesia in mice. Endomorphin 1 and 2 reduced C-fibre and and Aβ-fibre (endomorphin 1 only) responses after i.t. administration in rats.[16] In common with other opiates, endomorphins inhibit Ca^{2+} entry through voltage-sensitive Ca^{2+} channels (in NG108 cells)[17] and inhibit cAMP formation in cells expressing recombinant μ opioid receptors.[18] In addition, and in common with other μ-opioids, endomorphins 1 and 2 decrease cardiac output and total peripheral resistance and produce hypotension in rats and rabbits.[19–21] The clinical significance of these peptides in anaesthesia and pain management will need careful evaluation.

A fascinating new receptor–transmitter system, the orphan opioid receptor-nociceptin/OFQ, has recently been identified. The receptor, often termed ORL1, is found in the pain pathway but does not bind conventional opioids. The endogenous peptide nociceptin, or orphanin FQ, produces a range of effects in animals including analgesia, hyperalgesia and anti-opioid actions but this is controversial[22] (see also this issue). To help resolve the controversy, studies using the recently described orphan-receptor knockout mouse will be invaluable.[23] In January of this year Guerrini and colleagues described the first antagonist for the orphan receptor with affinity at the peripheral-type receptor,[24] and in March Okuda-Ashitaka and colleagues reported the isolation, from prepronociceptin, of nocistatin, which appears to reverse nociceptin action.[25] Further detailed studies with these peptides will clearly add to our understanding of this system *in vitro* and *in vivo*.

As well as these advances in basic pharmacology there is also continuing interest and research into the use of opioids in the clinical setting, some aspects of

Table 1 Classification of opioid receptors

Before 1992 Pharmacology	1992–1997 Cloning	1997 (IUPHAR) Unified
μ	μ (MOR)	OP$_3$
δ	δ (DOR)	OP$_1$
κ	κ (KOR)	OP$_2$

which are covered in this issue. These include introduction of the plasma-esterase-metabolized opioid remifentanil, the emerging use of peripherally acting opioid antagonists such as methylnaltrexone[26 27] and exploration of novel routes of opioid administration.

I hope that the articles in this issue may stimulate readers to enter a fascinating area of research, and also that the clinical holy grail[1] of quality analgesia without respiratory depression can become a reality.

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Novel routes of opioid administration

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In the early days of anaesthesia, opioids were traditionally given by the intramuscular and intravenous routes and other methods of administration were considered as novel. However, because of expanding interest in both acute and chronic pain over the past few decades, the anaesthetist routinely administers opioids via the oral, subcutaneous, rectal, intrathecal, extradural and transdermal routes. All these modes of delivery can now be considered as conventional, despite the vagaries of product licensing in some situations. In this short review, we shall consider three methods of opioid administration that can still be considered as novel: intranasal and inhalational administration and iontophoresis. Some may consider intra-articular administration as novel, but this has recently been reviewed in detail elsewhere.[20]

Intranasal administration

Intranasal administration is particularly familiar to the recreational abuser of opioids and central nervous system stimulants but it is less established in current clinical practice. Reliable absorption across the nasal mucosa depends on lipid solubility and has the advantage of avoiding first-pass metabolism. Table 1 shows the specific opioids and doses that have been administered intranasally and reported in the literature.

Intranasal opioids can be administered as either a dry powder or dissolved in water or saline. A specifically designed spray device has been shown to produce a wider distribution of drug compared with simple drops.[13] Butorphanol has been formulated in an intranasal metered-dose spray (0.25 mg)[26] and pethidine,[34] oxycodone[37] and fentanyl[35] have been diluted with saline and given via a pre-metered spray bottle. Sufentanil has been given with a 1- or 3-ml syringe,[16] nasal spray or nasal dropper,[43] and diamorphine as a 3% mixture with lactose via a straw[9 31] or in solution with a tuberculin syringe.[45]

Only a few investigators have reported the absorption pharmacokinetics of their preparations (table 1). Takala and colleagues[37] found that the mean (95% CI) bioavailability of oxycodone after intranasal administration was 46(25–67)%, with a median (range) t_{max} of 25 (10–240) min. In contrast, t_{max} for diamorphine absorption was achieved within 5 min in two studies.[9 31] Bioavailability was not measured in these studies but the relative potency of intranasal diamorphine compared with intramuscular was 50%. Haynes and colleagues[15] found that, after intranasal sufentanil 2 μg kg^{-1}, the range for plasma t_{max} was 1–30 min and analgesic plasma concentrations were maintained for at least 2.5 h. Streibel and others[35] did not measure the absorption pharmacokinetics of fentanyl 45 μg but found that intranasal fentanyl had a similar relative potency compared with i.v. administration (perhaps suggesting good bioavailability) and mean (SD) time to maximum post-operative analgesia was 26.3 (15.0) min compared with 20.2 (12.0) min after i.v. administration. Similarly, the same group[34] did not report the pharmacokinetics of intranasal pethidine absorption but when compared with subcutaneous injection, there was no significant difference in requirement or duration of analgesia.

Proposals for the clinical use of intranasal opioids include pre-operative sedation and post-operative pain control. Its use in children has been investigated particularly. For example, intranasal sufentanil produced a somnolent child and smooth induction of anaesthesia.[15 16 48] Providing adequate analgesia in the accident and emergency department for children with moderate to severe pain is particularly difficult. Wilson and colleagues,[45] in an open study, found that intranasal diamorphine provided analgesia as rapidly and efficiently as intramuscular morphine but with significantly better parent acceptability. All the parents whose children received intranasal medication described the episode as acceptable compared with 55% of those in the intramuscular group. Diamorphine 0.1 mg kg^{-1} was given in a constant volume of 0.2 ml via a 1-ml syringe. The solution was allowed to drop gently into one nostril.

Others[35] have reported that intranasal was as effective as i.v. fentanyl for the treatment of "severe" post-operative pain in more than 50 adult patients after a variety of general and orthopaedic procedures. When intranasal was compared with intermittent s.c. pethidine after orthopaedic surgery, pain scores and patient satisfaction were improved.[34]

There are few reported side-effects related specifically to the intranasal route of administration, presumably because, unlike midazolam, none of the opioids are particularly irritant. For example, 85% of children cried after intranasal midazolam compared with 28% of those receiving sufentanil as premedication for day-care anaesthesia.[48] However, pethidine was associated with a bitter, burning taste in 20% of

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Table 1 Opioids administered by the nasal route, with bioavailability and t_{max} where reported

Drug	Dose	Bioavailability	t_{max}	Reference
Oxycodone	0.1 mg kg^{-1}	46%	Median (range) 25 (10–240) min	37
Diamorphine	0.1 mg kg^{-1}			45
	6, 12 mg		Within 5 min	9, 31
Fentanyl	0.027 mg			35
Sufentanil	1.5, 3, 4.5 μg kg^{-1}			16
	2 μg kg^{-1}		15–30 min	15, 48
Alfentanil	0.54 mg			29
Pethidine	27 mg as required			34
Butorphanol	0.25, 0.5, 1, 2 mg			26, 19

Table 2 Opioids delivered by inhalation, with bioavailability and t_{max} where reported; *during mechanical ventilation

Drug	Dose	Bioavailability	t_{max}	Reference
Morphine	10, 20 mg			27
	10 mg	Mean (range) 17 (9–35) %*		7
	2 mg			4
	50 mg	Mean (95% CI) 5.5 (3.2–7.8) %	Within 10 min	24
	10, 25 mg			22, 23
	5 mg			21
	2.5, 5 mg			14
	5 mg			47
	80 mg		Approx. 10 min	25
	5–30 mg			11
Fentanyl	100, 300 μg		Approx. 2 min	46
	192, 477, 954 μg			17
Diamorphine	50 mg		Approx. 6 min (morphine)	25
Hydromorphone	1–20 mg			11
Codeine	15–60 mg			11

patients self-administering a nasal preparation after operation.[34]

Intranasal administration of opioids for postoperative pain relief is not likely to supersede other techniques such as patient-controlled analgesia. However, it may have a role in patients with difficult i.v. access and in the management of acute pain in children. Further work is required in this area.

Inhalational opioids

Although inhalation is considered as a novel method of administration in medicine, opioids have been inhaled for centuries. Investigations into this technique have been encouraged by the suggestion that inhalation is not just another method of systemic administration of opioids, but also a method of targeting specifically opioid receptors in the lungs. Using immmunoreactive techniques, opioid peptides have been detected in bronchial mucosal cells[5] and doses as low as 5 mg of nebulized morphine have been reported to reduce significantly the sensation of breathlessness in patients with chronic lung disease.[47] This has led some to speculate on the possibility of a true peripheral opioid action. However, a peripheral action is not accepted generally and any observed effects may be secondary to central actions, such as relief of anxiety or an effect on a central attenuation of the response to afferents from peripheral receptors.

The delivery by inhalation of several opioids has been investigated (table 2). In each case the drug has been administered by wet nebulization in a wide range of doses, concentrations and volumes (2–6 ml). Only a few authors have measured and reported absorption pharmacokinetics (table 2). On inhalation of morphine and diamorphine, morphine has been detected in the plasma after 1 min[25] with a plasma t_{max} for morphine after morphine and diamorphine inhalation of approximately 10 and 6 min, respectively. A similar t_{max} after morphine inhalation was found by Massood and colleagues.[24] Fentanyl is also absorbed rapidly (t_{max} approx 2 min).[46] Several factors can affect the bioavailability of inhaled opioids. These include nebulizer design,[8] amount of drug swallowed[7] and the inspiratory/expiratory ratio of the respiratory cycle.[12] Mean bioavailability of morphine has been reported as 17 and 5.5% with a wide variability (table 2).[7 24] The larger value was measured during morphine administration to patients receiving positive pressure ventilation.

Inhaled opioids have been investigated for several indications: dyspnoea at rest associated with severe heart or lung disease; exercise tolerance; pain after surgery; and the provision of analgesia in general practice. Effect on breathlessness and exercise tolerance in patients with severe dyspnoea has been studied widely but results are inconsistent. Young and colleagues[47] reported a marked improvement in exercise endurance in patients with severe lung disease (FEV$_1$ 0.4–1.4 litre) after inhalation of nebulized morphine 5 mg. However, several authors have reported no effect. For example, Beauford and colleagues[4] found no effect of morphine (maximum 10 mg) in a similar group of patients. In a comparison of inhaled morphine 10 mg and 25 mg with smaller doses of i.v. morphine, no difference could be detected.[23] Furthermore, two other groups[14 21] found no effect after the same doses used by Young and colleagues. In the latter study, only exercise tolerance was measured and not the subjective symptom of breathlessness. The potential for nebulized morphine to deliver easily administered analgesia in general practice has been investigated in a few subjects.[25] The authors concluded that the technique was suited for use in general practice but expressed concern regarding the inefficiency of the apparatus and unpredictable absorption.

There are fewer published data on the use of inhaled opioids for post-operative analgesia and the problems associated with absorption pharmacokinetics led Chrubasik and colleagues to reject it as a method for future study.[7] Worsley and colleagues[46] investigated the effect of fentanyl inhalation (100 and 300 μg) on pain scores in patients in the recovery room immediately after surgery. The study was not double-blind and involved a wide range of surgical procedures (from varicose veins to vagotomy). They reported an improvement in post-operative pain scores after inhaled fentanyl associated with plasma concentrations 95% lower than those regarded as analgesic. The authors speculated that the mechanism of analgesia during inhalation may differ from that associated with other methods of administration. The same group subsequently reported a double-blind study[17] and concluded that there was no evidence that this mode of delivery was more effective than other parenteral methods.

Problems related specifically to the method of drug delivery reported in the literature include the sensation of a bitter taste[27] with morphine and cough[17] and nasal pruritus with fentanyl.[46]

The inhalational route is non-invasive and is probably associated with rapid absorption. However, the large variation in absorption is a major disadvantage and there is little evidence for a local action on the lungs. Inhalational opioid delivery is not likely to become accepted as a method of postoperative pain control, but it is used by some palliative care physicians for symptomatic control of breathlessness.

Iontophoresis

The stratum corneum of the skin is an excellent barrier to transdermal transport of water and solutes; its integrity is crucial to the maintenance of homoeostasis and as a defence against bacteria. To penetrate this barrier in clinically significant amounts, drugs need to be of small molecular weight, lipophilic, uncharged and potent. Fentanyl and glyceryl trinitrate are examples of such drugs and their use is commonplace in modern medicine. Transdermal delivery avoids the problems of first-pass metabolism and provides a simple method of continuous parenteral administration.

Glyceryl trinitrate is an ideal drug for transdermal delivery (very lipid soluble, with rapid clearance) but fentanyl is less than ideal. The t_{max} for fentanyl absorption by this method is prolonged[10] and plasma half-life after removal of the patch is extended because of the formation of a deposit of fentanyl in the skin and surrounding tissue. Rapid and reliable changes to the delivery rate are not possible with this technique – a problem of little consequence in chronic pain but of vital importance in the acute situation.

Iontophoresis is a method of transdermal administration of drugs in an ionized state by electric current. The theory is simple. If a drug is applied to the skin in an electrode of the same charge as the drug (for example, lignocaine/anode) and an electric current is applied, the drug will pass with the current and be deposited not only superficially but in the deeper subcutaneous tissues. The circuit is completed by a drug-free electrode of opposite charge placed close to the active electrode. The efficiency and safety of this technique depend on several factors, such as current wave form and electrode design.[36]

Although interest in iontophoresis has waxed recently, it was originally described by Veratti in 1747 and again by Leduc at the beginning of the 20th century.[32] Leduc showed that iontophoretic application of strychnine to rabbits rapidly produced convulsions. When the polarization of the electrodes was reversed, no effect was observed.

To date, most of the interest in iontophoresis has concerned the administration of local anaesthetics, although other drugs have been investigated – for example, gonadotrophin-releasing hormone,[3] diclofenac,[42] acyclovir,[44] and nicotine.[6] It has been used for the administration of pilocarpine in infants as a diagnostic test for cystic fibrosis.[30] Evidence of deep penetration of lignocaine when given by iontophoresis was demonstrated by Irsfiel and colleagues,[18] who compared the effect of EMLA cream applied for 60 min under an occlusive dressing with iontophoretically-applied lignocaine (5% lignocaine 0.5 ml; 0.1–0.2 mA cm^{-2} for 10 min) on the pain on injection of hypertonic saline into an antecubital vein. They showed that both methods produced skin analgesia but only the iontophoretic technique abolished pain in injection. Recent work has shown the efficacy of the method in preventing pain on injection of propofol.[28]

There is some interest in the administration of opioids by this technique. The potential advantages of the method are illustrated by a study of fentanyl and sufentanil administration in rats.[38] Sufentanil and fentanyl (dissolved in an acetate buffer pH 5) were placed with the anode electrode on the skin of hairless rats and a direct current applied (0.17 mA cm^{-2}) between it and a nearby cathode electrode. There was a rapid achievement of sufentanil and fentanyl plasma t_{max} (1.5 h), with pharmacologically significant plasma concentrations as measured by plasma assay and changes in the tail flick test. The factors affecting the delivery of fentanyl by this technique have been investigated extensively and it is recognized that delivery is affected by the physicochemical nature of the drug and solution and the voltage, duration and nature (for example, exponentially decaying pulses *vs* square wave) of the current.[39–41]

The pharmacokinetics and pharmacodynamics of iontophoretically delivered fentanyl have been reported in five adult volunteers.[2] Current was applied

(1 mA and 2 mA) to a solution of fentanyl 2 mg ml^{-1} at a pH of 4.5. Mean (SD) t_{max} after 1 and 2 mA were 122 (14.4) min and 119 (7.4) min respectively. C_{max} values were 0.76 (0.2) and 1.59 (0.2) ng ml^{-1}. Morphine is the classical water-soluble opioid that is not absorbed transdermally. However, it is can be administered by iontophoresis and plasma concentrations after the application of 2 mA of pulsed direct current (2.5 kHz) have been reported in volunteers.[33] Morphine was detectable after 5 min with a t_{max} of approximately 1 h. Maximum concentration ranged from 11.4 ng ml^{-1} to 19.8 ng ml^{-1}.

There are few published data on the clinical use of opioids delivered by iontophoresis but morphine has been used for postoperative analgesia after total hip or knee replacement surgery.[1] Patients were stabilized on pethidine patient-controlled analgesia and, on the morning after surgery, devices delivering morphine hydrochloride or lactate solution were applied for 6 h. During this time, and up to 12 h after completion of iontophoresis, the active group used significantly less pethidine.

The delivery of fentanyl by iontophoresis has been investigated more extensively than that of other opioids. These data suggest that iontophoresis may enable transdermal administration with a rapid achievement of steady state and the ability to vary delivery rate. This would be potentially beneficial not only in patients suffering chronic pain with breakthrough symptoms but also for the treatment of acute pain – an indication where the simple transdermal patch was found wanting because of its prolonged t_{max} and the inability to vary the rate of administration.

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Peripheral and central mechanisms of pain

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Our understanding of nociceptive processing has progressed significantly in recent years, largely because of an improved understanding of afferent fibre physiology and synaptic processing in the dorsal horn of the spinal cord. These developments are the result of the use of several experimental approaches, including behavioural studies, *in vivo* and *in vitro* electrophysiology, molecular biology and anatomical studies.

It has become apparent that the responses of the spinal cord to afferent input are altered after persistent activation, that is, sensitization/excitation, of primary afferent nociceptors. Experimental models of peripheral inflammation and studies in man have been useful in providing information on the response of spinal cord neurones to persistent activation of nociceptors. They indicate that, far from being a simple relay in the pathway to the brain, the spinal cord processes nociceptive input in very specific ways that are not static, but change with time. These changes manifest themselves as an increased sensitivity of spinal cord neurones to afferent input and an expansion of peripheral receptive fields, termed spinal hyperexcitability. The excitability of spinal cord neurones is dependent on the balance of inputs from primary afferent nociceptors, intrinsic spinal cord neurones and descending systems projecting from supraspinal sites. An indication of neurotransmitter systems that may have an important role under these conditions comes from experiments that have measured the release of neurotransmitters and the effect of neurotransmitter receptor antagonists, and from those that have examined the expression of genes involved in neurotransmitter systems. Many of these genes are up- or down-regulated in models of inflammatory pain (and neuropathic pain), suggesting that they may be particularly important in initiating or maintaining spinal components of pain.

The potential importance of this type of research is in identifying possible new targets for analgesic therapy and in understanding the timing of events that contribute to the development of these hyperexcitability phenomena in the spinal cord. It is conceivable that timing the administration of drugs targeted at individual neurotransmitter systems (receptors or enzymes involved in neurotransmitter synthesis) to pre-empt or coincide with known changes in neurotransmitter gene expression may provide a useful approach to the management of pain.

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The nociceptive system

Peripheral nociceptors are distinguished from other sensory nerve fibres on the basis of morphology, conduction velocity and responsiveness to mechanical stimuli. Nociceptors have poorly differentiated terminals, slow conduction velocities (C fibres, $< 2.5 \text{ m s}^{-1}$ A-δ fibres, $2.5\text{–}20.0 \text{ m s}^{-1}$) and are normally activated by potentially damaging or damaging stimuli, that is, stimuli of strong to noxious intensity.

Primary afferent nociceptors terminate mainly in the superficial (C and A-δ fibres) but also in the deep (A-δ fibres) dorsal horn of the spinal cord, where they release several neurotransmitters. Glutamate, an excitatory amino acid (EAA) released from these central terminals of the nociceptors,[25,46] elicits fast synaptic responses in second-order neurones[42] that are mediated by at least two EAA receptor sub-types, the (±)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and the *N*-methyl-D-aspartate (NMDA) receptors, so called because they are activated by these selective ligands. A proportion of primary afferent nerve fibres also express and synthesize neuropeptides that are co-released with glutamate within the spinal cord. Substance P, neurokinin A and calcitonin gene-related peptide (CGRP), which are found in 20%,[29] 9% (joint afferents[18]) and 25–47%[19,30] of primary afferent nerve fibres respectively, but predominantly in nociceptors, are three such peptides. They are released in response to noxious thermal or mechanical stimuli or in response to electrical stimuli applied to sensory nerves at a stimulus intensity sufficient to excite C and A-δ afferent nerve fibres.[13,14,31]

Many dorsal horn neurones project to the brain, mainly in the spinothalamic, spinoreticular and spinomesencephalic tracts. On termination in these regions the information may be processed to produce a perception of pain or to elicit output that is relayed to the spinal cord by way of descending fibre tracts mainly originating in the medulla or cortex.

Responses of afferent nerve fibres and spinal cord neurones to persistent afferent input

ELECTROPHYSIOLOGICAL CHANGES

During peripheral inflammation nociceptors within damaged tissues are readily excited by non-noxious stimuli (allodynia) or show an enhanced response to noxious stimuli (primary hyperalgesia). This sensitization of nociceptors is produced by physical changes in the damaged tissues (oedema, synovial

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effusion, etc.) and by inflammatory mediators, for example, prostaglandins, serotonin and bradykinin, which alter the sensitivity of nerve endings to mechanical and thermal stimuli. In addition to the reductions in mechanical threshold, some nociceptors are also directly activated by the inflammatory mediators present, such that continuous low-frequency firing (~1.0 Hz) can be detected in the afferent axons of these nociceptors.[43]

Following the development of peripheral inflammation the responses of spinal cord neurones to peripheral stimulation are also altered. This has been demonstrated most conclusively in neurones located in the deep dorsal horn and ventral horn of the spinal cord, which receive input from both nociceptors and low-threshold mechanoreceptors, that is, wide-dynamic-range (WDR) neurones. As with primary afferent nociceptors, peripheral inflammation elicits a reduction in the mechanical threshold for activation of these neurones as the duration and intensity of the inflammatory lesion develop. The second change is an enlargement of the peripheral receptive fields,[17,32] which can be interpreted as increased sensitivity of spinal cord neurones to subliminal inputs from the periphery of the receptive field. Under normal circumstances WDR neurones have moderate-sized receptive fields most readily activated by mechanical stimuli applied to the centre of the receptive field. If the stimulus is applied nearer the edge of the receptive field the mechanical threshold for activation of the spinal cord neurone generally increases, indicating that the size of this synaptic input to that neurone is smaller. Stimuli applied to the edge of the receptive field do not elicit cell firing but may elicit sub-threshold responses (excitatory post-synaptic potentials (EPSPs)). When inflammation develops in the periphery, however, there is persistent firing in the afferent nociceptors, which continuously release a number of neurotransmitters into the synapses. It has been established that the amount of glutamate released into the synapse increases,[46] which will elicit rapid (AMPA-receptor dependent) and slower (NMDA-receptor dependent) EPSPs. Other neurotransmitters, such as substance P,[44] neurokinin A[21] and CGRP,[37] whose release is also continuous and is also increased under these circumstances, contribute to the prolonged depolarization of the post-synaptic neurone. This action is enhanced by the resistance of some neuropeptides, for example neurokinin A, to enzymatic degradation, which may mean that they persist in the synapse and that they may diffuse and act in a paracrine manner.

The net effect of the release of all of these neurotransmitters is to excite the neurone and move the membrane potential closer to threshold for the firing of action potentials. When in this condition the neurones are more sensitive to smaller inputs from low-threshold (tactile) and high-threshold (nociceptors) mechanoreceptors,[27,49] such as those in the subliminal regions of the receptive field. While the EPSPs evoked by stimulation of these regions fail to elicit cell firing under normal conditions, they now elicit action potentials because the depolarization required to move the resting membrane potential to threshold is reduced.

The result of this is that firing is elicited by stimulation of the former subliminal zone and the receptive field apparently expands. This is a form of spinal hyperexcitability (sometimes called central sensitization) and is the mechanism thought to underlie the phenomenon of secondary hyperalgesia. This phenomenon has been observed in a wide variety of experimental paradigms including acute[32] and more chronic models of joint inflammation[17] and in man.[1,49] Indeed, this expansion can be very marked, such that weak synaptic inputs from the contralateral hindlimb begin to excite neurones receiving input predominately from the ipsilateral leg.[45]

Experimental paradigms have been developed that enable one to examine spinal hyperexcitability and investigate the underlying pharmacology. If, in the normal animal, that is, in the non-inflamed state, trains of electrical stimuli are applied to sensory nerves at an intensity sufficient to excite C fibres or A-δ fibres or both, and the responses of spinal cord neurones are monitored by measuring neuronal activity directly with intracellular or extracellular electrodes or by recording motor outflow from the ventral roots or muscle (EMG activity), the phenomenon of wind-up can be observed.[10,48,52] This is an enhanced response of spinal cord neurones to successive stimuli in the train and occurs because of the summation of EPSPs (a single shock elicits an EPSP lasting several seconds), which results in a progressive depolarization and enhanced cell firing following each stimulus.[48] This is clearly a frequency-dependent effect and can be observed at stimulus frequencies as low as 0.5 Hz, a frequency that is not dissimilar to the background firing rate of sensitized nociceptive afferents. It is possible therefore that the wind-up paradigm mimics, in some respects, the situation observed in animal models of inflammation where spinal cord neurones are rendered hyperexcitable by persistent low-frequency input from sensitized afferent nociceptive fibres. Wind-up and central sensitization are not, however, identical processes although they share many features.[51]

PHARMACOLOGY OF SPINAL NOCICEPTIVE PROCESSING

Wind-up can be blocked by administration of NMDA receptor antagonists, for example, ketamine or AP-5, through a reduction in the magnitude and duration of these long-duration EPSPs elicited by single nerve shocks, thereby preventing summation and reducing cell firing.[48] Neurotransmitter receptor antagonists that selectively block the action of other primary afferent neuropeptides, for example substance P (NK$_1$[5,7,50]), also reduce wind-up when applied in the vicinity of spinal cord neurones, indicating that the pharmacology of wind-up is complex. Opioid peptides are also effective in reducing wind-up but only when applied pre-emptively,[8] presumably through activation of opioid receptors that are known to be present on the terminals of primary afferent nerve fibres (μ and δ subtypes) and on spinal cord neurones (μ, δ and κ subtypes). Opioid peptides probably exert their effects at one or both of these sites by blocking voltage-gated calcium channels that will prevent neurotransmitter release from primary afferent nerve fibres,[24] or by opening potassium channels[39] that will result in neuronal hyperpolarization, or both.

In man, electrical stimulation at an intensity sufficient to elicit pain also produces temporal summation.[2,40] In these studies electrical stimuli were applied to the skin and either EMG or M-VAS scores were recorded. The summation of these nociceptive responses can be blocked by NMDA receptor antagonists,[3,40] indicating that some similarities exist between the pharmacology of wind-up in man and in experimental paradigms.

Drugs acting at the same receptors are effective in preventing the development of neuronal hyperexcitability or in reversing it once it is established in experimental models of inflammatory pain, for example NMDA receptor antagonists,[33,45] NK$_1$ receptor antagonists,[35] NK$_2$ receptor antagonists[38] and CGRP receptor antagonists.[37] NMDA receptor antagonists administered pre-emptively, alone or in combination with other analgesics, in a variety of clinical paradigms, seem to produce signs of improved post-operative pain control.[4,9,15,26,40] Similarly, pre-emptive administration of morphine also improves post-operative pain control in man.[41] Both human and experimental data suggest that several neurotransmitter systems are involved in the initiation of spinal hyperexcitability, or are able to modulate it once established, or both.

NEUROCHEMICAL CHANGES IN THE SPINAL CORD

While electrophysiological measures of the changes in neuronal responsiveness and measurements of the release and actions of some neurotransmitters provide valuable information about the processing of nociceptive input, new information has become available from studies of gene expression in primary afferent nerve fibres and spinal cord neurones in models of inflammatory disease. These studies have shown that the genes encoding the sequence of some primary afferent neuropeptides are upregulated when a peripheral inflammation is induced. Two examples of these are the preprotachykinin gene, which encodes substance P, the endogenous NK$_1$ receptor ligand and neurokinin A, the endogenous NK$_2$ receptor ligand, and the gene encoding the sequence for CGRP. In Freund's adjuvant-induced monoarthritis in the rat, both genes are up-regulated[12] with a time course (2–3 weeks) that mimics closely the physical changes (swelling) in the joint. This also results in an increase in the amount of these peptides in the dorsal root ganglia[19] and presumably to increased release within the spinal cord, although this has not been measured in this model of arthritis. One could argue that this increase in gene expression occurs so as to synthesize more peptide as part of the response to increased activity in the afferent nerve fibres. This is not true, however, for two other neurotransmitter systems, the endogenous opioid and eicosanoid systems in intrinsic neurones of the spinal cord.

In the same model of inflammation, preprodynorphin (and to a lesser extent preproenkephalin) gene expression is up-regulated in the spinal cord[11,25] but with a quite different time course to that observed for the primary afferent neuropeptide genes. In this case there was rapid (3–4 h) induction of the preprodynorphin gene as measured by mRNA synthesis[11] but the increases in dynorphin (1-8) synthesis did not occur for 2–5 days,[23] which is significantly delayed compared with the time course of substance P synthesis.[19] This indicates that an endogenous pain control mechanism is switched on at a defined time after the induction of arthritis to regulate substance P activity.[47] Cyclo-oxygenase (cox)-2, a gene that encodes the protein that converts arachidonic acid to the prostaglandin precursor molecule PGH$_2$, is up-regulated but only very acutely, that is in the 24–48 h after the induction of arthritis.[6,16,22] Prostaglandins, which are important in spinal nociceptive processing,[28,34,36,52] seem, therefore, to have a role as neurotransmitters or neuromodulators only during a very defined time period.

It is clear that we still have much to learn about these changes in gene expression in the spinal cord and how they are induced, the role of immediate early genes such as *c-fos* and *c-jun* and why they occur at different times. Only by understanding the timing of induction and the precise roles of both excitatory and inhibitory elements in the nociceptive system shall we be able to gain a better insight into the complexities of pain processing. One hope is that a better understanding of the roles of these different neurotransmitter systems at different stages of inflammatory disease may help with the identification of novel therapeutic targets and with the timing of administration of analgesic drugs.

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Molecular mechanisms of opioid receptor signal transduction

B. Jordan and L. A. Devi

The analgesic and antidiarrhoeal uses of opium were known to the Sumerians and predynastic Egyptians. During 5000 years of medicinal use, opium has become associated with countries, cultures and prominent individuals, and through several modifications, remains an extensively used analgesic and addictive drug. Morphine, the principle active compound in opium, was first isolated by the German chemist Friedrich Sertuner in 1805. Replacing opium in therapy, its high potential for abuse was quickly discovered. Attempts to develop safer morphine analogues have spawned many compounds including heroin, a compound initially hailed as a safer and less addictive option. To date, however, no compound has proven free from a liability to be abused.[11] Nevertheless, the search for safer morphine analogue led to the synthesis of the first antagonist, naloxone, and several other non-endogenous agonists and antagonists, effectively creating the first tools for opioid research. While pharmacological characterization is crucial, the search for safer analgesics requires a thorough understanding of the mechanisms of cellular loss of responsiveness. The recent cloning of opioid receptors has created a new wave of research in the development of opioid tolerance, which may lead to a better understanding of this phenomenon.

Identification of opioid binding sites

Starting as early as 1954 with the experiments of Beckett and Casy, the concept of pharmacologically relevant opioid binding sites emerged and strengthened, with their discovery in mammalian brain.[77 94 100] Research in the field has led to the identification of three distinct opioid receptors, μ, δ and κ, each possessing unique pharmacological and physiological properties.[35 58 93 113] Although the existence of receptor subtypes has been proposed (for reviews see references 102 and 103), few data exist to support this. The first endogenous peptide ligands were discovered in the mid-1970s.[9 21 34 42 73] Opioid ligands include enkephalins, dynorphins and endorphins, which are derived, in mammals, from three larger precursors: proenkephalin A,[71] prodynorphin,[47] and pro-opioimelanocortin, respectively.[68] While several key experiments have resulted in extensive pharmacological characterization of opioid receptors, the presence of heterologous receptor populations and low expression in cells have always hampered further receptor studies. Recent cloning of the μ, δ and κ opioid receptors[16 27 49 117] has allowed many questions to be answered by expressing receptor cDNAs in cell lines that lack endogenous receptors. While these studies have yielded invaluable data on receptor structure, the molecular nature of desensitization remains largely unresolved. A connection between cellular desensitization and drug tolerance has led countless scientists to puzzle over the molecular mechanisms controlling cellular adaptation. The long-term effect of agonists on the molecular mechanisms of signal transduction are important in understanding tolerance.

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Biological effects of receptor activation

Agonist binding and subsequent receptor activation initiate a cascade of events that result in a varied array of biological effects. These include analgesia, miosis, bradycardia, general sedation, hypothermia, insensitivity and depression of flexor reflexes. The best studied role of opioids is in pain control, in which opioids are known to inhibit neurotransmitter release from dorsal root ganglion projections in the dorsal horn of the spinal cord.[59 65 116] Opioids are also known to modulate endocrine processes[33 60 89] and the immune system.[10 86] This diversified repertoire prompts the obvious question: How can this system affect so many different processes? The cloning of opioid receptors confirmed that they belong to the G-protein-coupled receptor superfamily and therefore transduce their signals through interaction with guanine nucleotide-binding proteins. While knowledge of effector regulation by opioids precedes receptor cloning, the specificity involved in receptor regulation of these remains unclear. This review will describe the events leading to opioid-induced effector activation in the order they are presumed to occur.

Formation of receptor–ligand complexes

The biological effects exerted by opioid receptors begin with the formation of a specific receptor–

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ligand complex. Fuelled by the potential for discovering novel opioid ligands, many groups have searched for receptor domains involved in ligand selectivity. Comparison of the deduced primary structure of the opioid receptors shows a 65–70% homology between the three receptors, with highest homology among the transmembrane domains, intracellular loops and a small portion of the C-terminal tail near TM7. The second and third extracellular loops, and the N- and C-terminal tail, are highly divergent. To determine the regions of the receptors involved in ligand selectivity, initial studies relied on chimeric μ/κ or δ/κ receptors. Experiments swapping domains of the second and third extracellular loops found that these were important in ligand binding determination. Studies of chimeric receptors have shown that the third extracellular loop of δ opioid receptors,[107] the first[108] and third[63] extracellular loops of the μ opioid receptor, and the second extracellular loop and top half of the fourth transmembrane domain in the κ opioid receptor[52,61,108,115] are important in their respective agonist selective binding. These studies, however, were unable to reveal key residues in the receptor binding sites.

To determine the critical amino acids necessary for agonist and antagonist binding, receptor mutants with selective single amino acid substitutions were used. Aromatic transmembrane residues at positions 129 and 308,[3] amino acids at positions 284, 296 and 297[106] and 95[53] of the δ receptor are all apparently necessary for binding of δ-selective ligands. Minami and colleagues[62] identified a single residue, Lys108, that allows selective μ agonists to bind to δ receptors when mutated. Claude and colleagues[20] found that the mutation of a single conserved serine in all three receptors (Ser196 at μ, Ser177 at δ and Ser187 at κ) confers full agonist properties on classical antagonists such as naloxone. While several residues have been found to be critical in the formation of a ligand–receptor complex, studies aimed at finding critical residues for receptor activation have been limited.

The association between opioid receptors and G-proteins was reported in the mid 1970s. Early studies showed that guanine nucleotides specifically decreased agonist binding in brain membranes[5] and neuroblastoma X glioma (NG108-15) hybrid cells.[6] It was noted that opioid receptors exist in two different affinity states depending on the presence or absence of guanine nucleotides. Detailed kinetic studies showed that the addition of GTP caused an increase in both agonist association and dissociation rates, but a greater increase in the dissociation rate.[17] Evidence of naloxone-reversible, GTP-dependent inhibition of adenylyl cyclase by morphine and opioid-stimulated GTPase activity in NG108-15 cell membranes provided further evidence for G-protein coupling of opioid receptors.[7,54,92] GTPase activity was initially associated solely with inhibition of adenylyl cyclase. However, regional differences between the distribution of GTPase activity and adenylyl cyclase inhibition were later reported.[30] Opioid-induced GTPase activity is pronounced in hippocampus, cortex and striatum, while inhibition of adenylyl cyclase appears to occur in striatum and frontal cortex. This suggests that agonist-induced GTPase activity is not only responsible for adenylyl cyclase regulation, but also for the regulation of other effector systems. This evidence later formed the basis for establishing that opioid receptors couple to multiple effector systems.

Opioid regulation of cyclic AMP

Cyclic AMP regulation by opioids was found in many cell lines and quickly became the trademark effect of opioid activity. Initially found in neuroblastoma X glioma cell lines by morphine treatment,[92] adenylyl cyclase inhibition has been demonstrated in many cells expressing opioid receptors. This effect required both Na^+ and GTP, like most other inhibitory receptor systems,[7] and suggested the participation of inhibitory G_i-proteins. The role of G_i inhibitory trimeric G-proteins was proposed and confirmed in NG108-15 cells by the abrogation of coupling by pertussis toxin.[40] Pertussis toxin (PT) can ADP-ribosylate and inactivate the inhibitory function of the α_i subunit, thus removing the inhibitory component of the pathway. Together with cholera toxin, which can ADP-ribosylate and thus inactivate the stimulatory function of the $G\alpha_s$ subunit, these compounds have proven invaluable in the identification of Gα subunit association with receptors. Adenylyl cyclase inhibition remains the effect most widely monitored to study acute and long-term effects of agonist treatment. To date, all cloned opioid receptors have been expressed in cell lines and found to inhibit this effector.[44,56,114]

Ion-channel regulation

Ion-channel regulation has further expanded the spectrum of opioid-induced biological effects. All three cloned opioid receptors couple to various Ca^{2+} channels (for a review see reference 78). These effects have been studied in a variety of cell types.[41,72] Opioids can inhibit N- and P/Q-type Ca^{2+} channels in nucleus tractus solitarius[84] and T-type Ca^{2+} channels in primary cultured dorsal root ganglion preparations.[87] The cloning of several voltage-gated Ca^{2+} channels allowed several teams to express both opioid receptors and Ca^{2+} channels in Xenopus oocytes. From this, a specific Ca^{2+}-channel α subunit involved in opioid receptor coupling has been identified.[8] Piros and colleagues have shown that agonist-stimulated μ and δ receptors inhibit DHP-sensitive L-type Ca^{2+} channels.[79] A recent study found that κ agonists modulate Ca^{2+} currents in isolated neuroendocrine nerve terminals.[88] Opioid receptors are also known to regulate inwardly rectifying K^+ channels. Experiments have shown agonist-mediated K^+ channel regulation in Xenopus oocytes expressing both opioid receptors and K^+ channels.[38] Another study in lower vertebrates reveals that opioid receptors can activate K^+ GIRK1 inwardly rectifying channels.[25] Although K^+-channel activation appears to be the norm, opioids can inhibit K^+-channel activity in the F-11 cell line.[22,28] Opioids also have measurable effects on Na^+/H^+ exchange.[43]

Secondary responses

In some cells, opioids can increase intracellular pools of Ca^{2+} by releasing intracellular stores. In these cells, phospholipase C is activated upon agonist stimulation that induces the formation of the intracellular messengers IP_3 and DAG. IP_3 then promotes the release of Ca^{2+} from stores. However, information about opioid-induced phosphoinositol turnover is sparse and sometimes contradictory. Although one study has shown that κ opioid receptors stimulate phosphoinositol turnover in rat hippocampal slices,[76] another has shown that κ receptors can inhibit GTPase-activated phospholipase C activity in guinea pig cerebellum.[64]

Much work has gone into characterizing these secondary responses, yet little has been identified in terms of the signal transduction pathways generated from them. Opioids can provide mitogenic signals in a variety of cell lines. DADLE treatment of rat-1 fibroblasts expressing δ opioid receptor activates the p42 and p44 isoforms of MAP kinase — presumably a mitogenic signal leading to an increase in DNA synthesis.[112] Opioid regulation of protein phosphorylation has also been observed. Although phosphorylation is common in brain membranes, several studies have shown opioid-specific inhibition of protein phosphorylation. Enkephalin treatment of brain membranes inhibited the phosphorylation of two membrane proteins of 47 kD and 10–20 kD (for review see reference 26). Nestler and co-workers[70] have shown increased cAMP protein kinase activity in rat locus coeruleus in response to prolonged morphine administration.

Receptor–Effector association

The existence of multiple effectors and biological responses mediated by opioids obviates the need for multiple signalling mechanisms. Opioid receptors expressed in cell lines have been shown to couple to a variety of trimeric G-proteins. Considering that receptor-activated effector selectivity is most probably mediated by these, a considerable amount of work has been carried out in to identify specific G-protein subunits associated with individual receptors. Presently, opioid receptors are thought to couple to G_i,G_o,G_q,$G_{(z/x)}$ and presumably G_s G-protein subunits. The inhibitory actions of opioids on adenylyl cyclase involve both G_i and G_o proteins. G_q, which has been implicated in κ-mediated analgesia,[96] may be important in phospholipase C activation. Apparently G_q mediates Ca^{2+} release in cardiac myocytes by this mechanism.[98] There are also several instances where GTP-sensitive binding is not fully decreased by pertussis toxin, suggesting involvement of not only $G_{(z/x)}$ but possibly also G_s proteins. Opioids exhibit stimulatory effects in certain instances (for a review, see reference 95). For example, there is evidence to suggest that opioid receptors may stimulate adenylyl cyclase.[15] In F-11 cells derived from dorsal root ganglia, opioids stimulate cAMP accumulation through G proteins sensitive to cholera toxin.[22 28]

A truly daunting task is establishing receptor-specific G-protein subunit association among the different receptors. Coimmunoprecipitation studies using transfected CHO cells have shown that the δ receptor associates with $G_{\alpha i1}$, $G_{\alpha i3}$ and $G_{\alpha o}$ in the native state, and dissociates from $G_{\alpha i1}$ and $G_{\alpha o}$ and associates with $G_{\alpha i2}$, upon agonist activation.[57] Studies using CHO cells transfected with the κ opioid receptor have suggested that this receptor associates with $G_{\alpha i3}$, $G_{\alpha i2}$ and $G_{\alpha o2}$.[80] Similar G-protein subunit distributions have been reported for μ and δ receptors.[15 81] Although these experiments suggest that there are no receptor-specific associations with G-protein subunits, recent work shows that $G_{(z/x)}$ subunits insensitive to pertussis toxin act preferentially with μ receptors in the periaqueductal grey of mouse brain.[31] Furthermore, while antibodies directed towards $G_{\alpha i2}$ subunits blocked GTPase activity by all opioids, antibodies directed towards $G_{(z/x)}$ blocked Pi (inorganic phosphate) release promoted by DAMGO and only slightly by δ agonists in periaqueductal grey.[32]

G subunit association studies have yielded conflicting results. Some studies have demonstrated specific receptor–G subunit association patterns that are similar for all opioid receptors, suggesting slight differences in receptor selectivity for G_α subunits among the different opioid receptors.[81]

Importantly, receptor-specific activation will lead to a specific biological response. G_α subunits may mediate such selectivity, as shown by the fact that only anti-$G_{\alpha o}$ antibodies can decrease Ca^{2+} current inhibition mediated by dynorphin A in dorsal root ganglia neurons.[110] Although G protein subunits may be the basis of response specificity, activation signals can be further tailored by a vast and emergingly complicated pathway. Mammalian cells may express up to nine forms of adenylate cyclase, inhibition of this effector being the primary method to detect opioid activation. This multiplicity of adenylyl cyclase isoforms may further target cAMP responses.[39] Thirty forms of enzymes exhibiting cAMP phosphodiesterase activity have also been identified. Moreover, cell signalling has been enormously complicated by evidence of adenylyl cyclase and other effector regulation by β γ subunits of G-proteins. Both β and γ subunits can inhibit adenylyl cyclase, stimulate phospholipase C and activate inwardly rectifying K^+ channels (reviewed in references 9 and 66). With more than five different β subunits and six γ subunits, a G-coupled protein receptor may selectively couple to any one of the permutations arising from the variety.[69] As an example, somatostatin receptors inhibit voltage-gated Ca^{2+} channels via $\alpha_{o2B}\beta_1\gamma_3$.[31] The situation may therefore be far more complex than initially imagined.

Ligand-induced conformational changes

Ligand-induced conformational changes may also play a role in receptor-induced biological responses. Evidence of this may lie in the puzzling findings that agonists with similar affinities can have different potencies.

An interesting study found that the delta-selective antagonist ICI-174,864 could potentiate forskolin-induced cAMP accumulation in HEK-293 cells transfected with the delta receptor.[18] These cells otherwise exhibited normal inhibition of adenylyl cyclase by (D-Pen2,D-Pen5)enkephalin. Morphine is unable to internalize the μ receptor in transfected cells while retaining the ability to inhibit adenylyl cyclase.[48] One study has shown that while the specific agonist U69,593 was able to cause receptor down-regulation of κ opioid receptor expressed in CHO cells, the non-specific opioid agonist levorphanol did not.[4] These results suggest that agonist-induced conformational changes are important in receptor regulation, which may be related to signal termination. It is not unreasonable to suggest that different agonists could have different effects on G-protein coupling, leading to different biological responses. Further structural studies may yield answers to this question.

Spatial aspects of response modulation

Although three opioid receptors, several possible receptor subtypes, G α, β and γ regulation and ligand-induced modulation suggest that an enormous number of factors is involved in the activation of a specific response, there may be a simpler explanation. Most studies are conducted in transfected cells containing several, and not a physiologically "select" group of G proteins, thus disregarding G-protein availability and spatial considerations. Few processes occur in isolation or irrespective of the spatial location of factors involved in signal transduction and termination. Specificity could simply be a function of protein availability. Mammalian cells have the option of expressing any one of nine isoforms of adenylyl cyclase and 30 forms of enzymes with cAMP phosphodiesterase activity, making specificity an act of presence. Spatial relevance within membrane limits has been demonstrated in an elegant study by Wilding and colleagues.[109] By simultaneously recording the channel activity within a patch and in the whole cell, they showed that bath applications of DAMGO on the cell, and not inside the patch, affected the whole-cell Ca^{2+} currents and did not affect Ca^{2+} channel activity within the patch. The inhibition of Ca^{2+} channels by DAMGO treatment therefore occurs only between closely associated opioid receptors and Ca^{2+} channels. Although a direct interaction between the G protein and the adjacent channel is probably responsible for such spatial regulation, direct interaction between receptor and channel is not an unreasonable suggestion.

Agonist-induced opioid desensitization

Once an intracellular message has been sent, opioid receptors will cease to translate extracellular messages. This is a crucial event in the regulation of extracellular signals via G-protein-coupled receptors. Cellular responses to stimulation are usually rapidly decreased or terminated to return to homoeostasis. These concepts are extremely important as the principles of cellular adaptation are thought to govern drug tolerance. While we have extensive knowledge of how G- protein-coupled receptors become desensitized to their environment, surprisingly little is understood about the mechanisms of agonist-induced opioid desensitization.

Densensitization is defined as a loss of function under prolonged exposure to an agonist. This suggests that any of the factors involved in effecting a biological response (effectors, receptors and messengers) may be subject to regulation. Volumes of information exist regarding cellular desensitization to opioids. Most of this work has been performed by measuring the attenuation of secondary responses upon agonist stimulation. By far the most studied opioid-induced cellular attenuation is that of adenylyl cyclase activity. Several early studies on desensitization of adenylyl cyclase inhibition were performed on cells exposed to prolonged morphine treatment. An initial loss of intracellular cAMP concentrations followed by a gradual increase in cAMP levels was observed in these experiments. These effects were receptor mediated because the addition of antagonists could restore cAMP levels. Interestingly, if morphine was removed or an antagonist added after 12 h, cAMP concentrations increased to higher than original levels. This was proposed to be the cellular basis for opiate withdrawal (a transient cAMP overshoot). Several other studies have shown that prolonged treatment with agonist reduces the receptor-ligand affinity and uncouples the system from adenylyl cyclase. In NG108-15 cells, 1 h of DADLE treatment was enough to desensitize GTPase activity by 65% but adenylyl cyclase activity was decreased only 20%, suggesting that GTPase activity is involved in other effects in addition to adenylate cyclase inhibition.[105] It is interesting that while studies have found strong evidence of δ and μ receptor uncoupling from adenylyl cyclase, there are conflicting data on the κ opioid receptor. Several reports indicate that while prolonged agonist treatment alters κ-specific ligand affinity, κ receptors do not undergo desensitization as measured by inhibition of adenylyl cyclase. These studies have been performed in the R1.1 mouse thymoma cell line[46] and in transfected CHO cells.[2] Other studies measuring the desensitization of electrophysiological effects have shown the contrary. Prolonged treatment of κ agonist U50, 488 on AtT-20 cells transfected with κ receptors resulted in the uncoupling of the receptor from an inwardly rectifying K^+ ion channel.[99]

MECHANISMS OF DESENSITIZATION

Although desensitization has been observed extensively, little is understood about the mechanisms by which it occurs. A system may become desensitized by global or local regulation or, more likely, by both. There are several important questions that must be addressed. Do opioids lose their ability to inhibit adenylyl cyclase because of effector inactivation? Or are cellular GTP levels decreased? Do the receptors themselves desensitize? If they do, does this involve structural modifications or simply regulation of receptor quantities? While most of the signalling attenuation may be directly related to the desensitization of the opioid receptor, this could not explain the ability of μ and δ agonists heterologously to desensitize cells. Prolonged μ agonist treatment of transfected cells not only rendered the system unable to activate K^+ channels upon further DAMGO addition, but also upon addition of MK 678, a somatostatin agonist. This suggests a global desensitization of the cell upon μ agonist treatment. Adenylyl cyclase may therefore become uncoupled not because of receptor desensitization but because of a global regulation of key factors.

While it seems trivial to discuss receptor desensitization when tolerance exists at the level of the cell and therefore the organism, drugs are being designed that reversibly bind to receptors without triggering cellular adaptation. If receptor desensitization triggers a generalized cellular adaptation, it will be important to separate and understand the individual events leading to the cellular loss of response to opiates. The apparent inability of κ opioid receptors to become desensitized after prolonged agonist treatment may be related to the relative low abuse liability associated with κ agonists.[83] As a thorough description of desensitization is beyond the scope of this article, we shall describe the mechanisms of receptor regulation that may be crucial to cellular adaptation. Opioid receptor regulation is fundamental for signalling control and involves internalization, down-regulation and possible receptor modifications.

MECHANISMS OF OPIOID RECEPTOR REGULATION

Agonist-induced receptor internalization and down-regulation are crucial parts of receptor regulation and may form the basis of cellular adaptation to acute and long-term agonist treatments.

Agonist-induced rapid internalization

Demonstration of agonist-induced rapid internalization of other G-protein-coupled receptors[111] suggested a similar mechanism of receptor regulation for opioid receptors. Opioid receptors expressed in heterologous cells undergo rapid internalization upon agonist treatment; approximately 50% of the receptors are internalized within 6 min, as measured by flow cytometry.[1 48 101] The rapid internalization of μ receptors in response to high-affinity agonists such as etorphine has also been observed in neurons *in vivo*.[97] The agonist-mediated internalization is homologous because δ opioid receptors internalize in response to δ receptor selective ligands and not to μ or κ receptor selective ligands and vice versa.[45] It is interesting that κ opioid receptors do not exhibit rapid internalization in response to treatment with high-affinity agonists such as etorphine.[45]

Little is known about the molecular mechanisms of this rapid internalization or the domains of the receptor involved in this phenomenon. We have recently found that δ opioid receptors exist as a dimer and undergo agonist-mediated monomerization.[23] Receptor monomerization precedes internalization, suggesting that agonist-induced monomerization may be a prerequisite for receptor internalization.[23] The C-terminal tail is necessary for dimerization and internalization, as the deletion of a portion of the C-tail results in a loss of both dimerization and internalization.[101] Mutation of any one of the serine/threonine residues in the C-tail results in significant loss of internalization, suggesting that these residues play an important role in modulating receptor conformation and thus affecting internalization.[98] A recent study has found that a nine-residue truncation of a Ser/Thr-rich domain unique to the C-terminus of μ receptors results in a constitutively internalizing and recycling mutant.[90] Taken together, these studies underscore the importance of the C-tail in opioid receptor internalization.

Receptor down-regulation

Receptor down-regulation is an important method by which cells become desensitized to prolonged agonist treatment. It is thought to cause a development of drug tolerance and may result from alterations of the rates of degradation and synthesis. Down-regulation is characterized by a generalized loss of both cell-surface and intracellular receptors. Prolonged antagonist treatment is known to have opposite effects mediating an upregulation of opioid receptors. Down-regulation of opioid receptors has been demonstrated in whole animals, neuronal cell lines and transfected cells.[74 91] Although long-term regulation of opioid receptors is thought to proceed from modulation of mRNA synthesis, this is still largely disputed. One study found that morphine treatment caused a significant decrease in μ-opioid receptor mRNA in basal hypothalamus, while leaving these mRNA levels unchanged in the preoptic area and thalamus.[85] Another study found that a marked down-regulation of δ opioid receptor binding sites after a 24-h treatment was not accompanied by a decrease in receptor mRNA levels in the thalamus.[12] A third study found that prolonged etorphine treatment down-regulates both the δ opioid receptor binding sites and mRNA levels in NG108-15 cells.[50]

While the molecular basis of down-regulation is not well understood, a recent study has implicated a receptor/G-protein complex as a necessity for down-regulation.[14] This study found that μ opioid receptors required a high-affinity G/complex formation to internalize and down-regulate, as assessed by the ability of pertussis toxin to block internalization. Surprisingly, this study also found that δ opioid receptor down-regulation was not affected by pertussis toxin treatment.

Phosphorylation may also be important in receptor down-regulation; this is shown by mutations of Thr353 of the carboxy tail of the δ opioid receptor that markedly affect down-regulation.[24] Receptor inactivation by phosphorylation has been reported in several G-protein-coupled receptors, but remains unclear in the opioid system. Several studies acknowledge phosphorylation of opioid receptors, yet the role of this modification in receptor regulation or activation is not clear.[36 67 75] The regulation of β-adrenergic receptor and other G-protein-coupled receptor levels by phosphorylation suggests that this is likely for opioid receptors. Phosphorylation by G-protein-coupled receptor kinases (GRKs) or cAMP responsive kinases or both could play a significant part in receptor down-regulation.

Physiological relevance of studies of the opioid system

Now that receptor cloning has made transfected cell lines a convenient method by which to study the opioid system, the impending physiological relevance must be carefully assessed. One must note that high expression systems are non-physiological and have increased populations of spare receptors, a phenomenon that may alter pharmacological studies. Several studies have shown the important effect of spare receptor populations on agonist affinity. One study has shown that the irreversible blocking of 95% of opioid receptor binding sites by β-chlornaltreaxamine (β-CNA) did not alter the inhibition of adenylyl cyclase as mediated by opioid agonists.[29] Furthermore, it has been shown that the receptors exist in three different affinity states, not only as a function of GTP and Na^+, but also as a function of receptor occupancy.[55] Desensitization studies measuring inhibition of adenylyl cyclase after prolonged agonist treatment have often neglected the presence of spare receptors. The presence of many unoccupied receptors, each with the ability to inhibit adenylyl cyclase, may yield ambiguous clues as to the specific desensitization of the opioid receptor. More factors to complicate desensitization studies lie in the broad subject of opioid peptide regulation, which is beyond the scope of this review.

In summary, the complexity of the opioid system was widely understood even before the receptors were cloned. The emergingly complex functions of trimeric G-proteins and other effector systems have provided many challenges for all G-protein coupled receptors. Although the existence of opioid receptors has been recognized for almost 30 years, exploration of receptor regulation is still at an early stage. Future work should unravel unanswered questions and possibly lead to an explanation of the molecular mechanisms of opioid tolerance.

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Stimulatory effects of opioids

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Opioid receptors

Opioid receptors exist as three principle types, known as μ, δ and κ and have been recently reclassifed by an International Union of Pharmacology subcommittee as OP1(δ), OP2(κ) and OP3(μ).[27] All three receptors have been cloned,[29 45 87 99] and have pharmacological characteristics consistent with those of endogenous receptors.[46] Multiple isoforms of each subtype have been proposed on pharmacological grounds but this remains controversial, as no subtypes have been identified using molecular biology techniques, although the possibility of post-translational modification of a common gene product remains.

Opioid receptors belong to the family of guanine-nucleotide-binding protein (G-protein) coupled receptors, consisting of seven transmembrane-spanning domains, an extracellular N-terminus, and an intracellular C-terminus. Such cell surface receptors have no direct contact with their final effector molecules. In this process receptors relay information via G proteins to activate effector proteins (fig. 1).

G proteins are heterotrimeric membrane-associated proteins consisting of α, β and γ subunits. They are able to activate effector enzymes by a relatively straightforward process, the "G protein cycle" (fig. 2). Historically G proteins are classified using two types of bacterial toxin, pertussis (PTX) and cholera (CTX). Pertussis toxin adenosine di-phosphate (ADP) ribosylates inhibitory G proteins (eg.G_i) and prevents interaction with the effector molecule. Cholera toxin prevents the GTP (Guanine–triphosphate) hydrolysis to GDP (Guanine–diphosphate) and therefore irreversibly activates α-GTP of stimulatory G proteins (G_s). However, the use of G-protein subunit-specific antibodies has more accurately defined this classification. (For a review on G proteins, see Neer.[64])

Both α and βγ subunits are able to activate G-protein-linked second-messenger systems. There are at least 16 types of α subunit isoforms, along with at least seven β and five γ isoforms, which allow for great diversity in G-protein signalling pathways. Common opioid receptor–G-protein-linked systems include adenylyl cyclase–cyclic adenosine monophosphate (cAMP), and phospholipase, C (PLC)–inositol 1,4,5 trisphosphate (Ins(1,4,5)P3)-Ca^{2+}. Adenylyl cyclase is the membrane-bound enzyme, of which there are at least eight isoforms, responsible for the conversion of adenosine triphosphate (ATP) to cAMP, which is in turn able to activate cAMP-dependent protein kinase A (PKA).[20] This enzyme is responsible for phosphorylation of specific cellular proteins, such as intracellular calcium-release channels. Hydrolysis of phosphatidylinositol 4,5 bisphosphate (PIP_2) by the membrane-bound enzyme PLC yields the second-messengers Ins(1,4,5)P_3 and diacylglycerol (DAG). Ins(1,4,5)P_3 is a diffusable second-messenger that can release calcium from specialized intracellular stores[33] (fig. 3).

The released calcium may then be involved in a wide range of events; for example, it may bind to calcium-binding proteins such as calmodulin, or cause further release of calcium. DAG may then be cleaved to produce arachidonic acid or cause the activation of protein kinase C (PKC). This enzyme also phosphorylates cellular proteins, such as ion channels in neurones.[52]

Opioids and neurotransmitter release

Opioids produce their analgesic effects via an inhibition of excitatory neurotransmission that involves substance P and glutamate. This is achieved by co-ordinated changes at a cellular level, namely closure of voltage-sensitive calcium channels, activation of potassium currents, resulting in slowing of the action potential, and a reduction in cAMP, which may inhibit the inwardly rectifying cation current I_h,[40] resulting in a reduction in neuronal firing (for a review on opioid inhibition of neurotransmitter release see Leslie[51] and fig. 4).

Opioids have also been reported to produce stimulatory effects on neurotransmission and neurotransmitter release, as discussed in a review by Sarne and colleagues.[71] Enhancement of neurotransmitter release by opioids was first explained as a suppression of opioid inhibition or "disinhibition". For example, the stimulatory effect of opioids on acetylcholine release from the caudate nucleus was suggested to result from presynaptic suppression of an inhibitory dopaminergic system.[92] More recently, direct stimulatory actions of opioids have been shown in a variety of tissues. Opioids increase adenosine secretion from spinal-cord synaptosomes,[10] increase release from dopaminergic neurones,[14 26]

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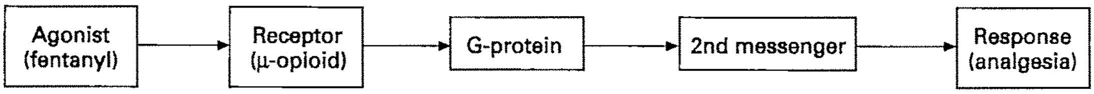

Figure 1 The process of signal transduction, with specific examples shown in parentheses.

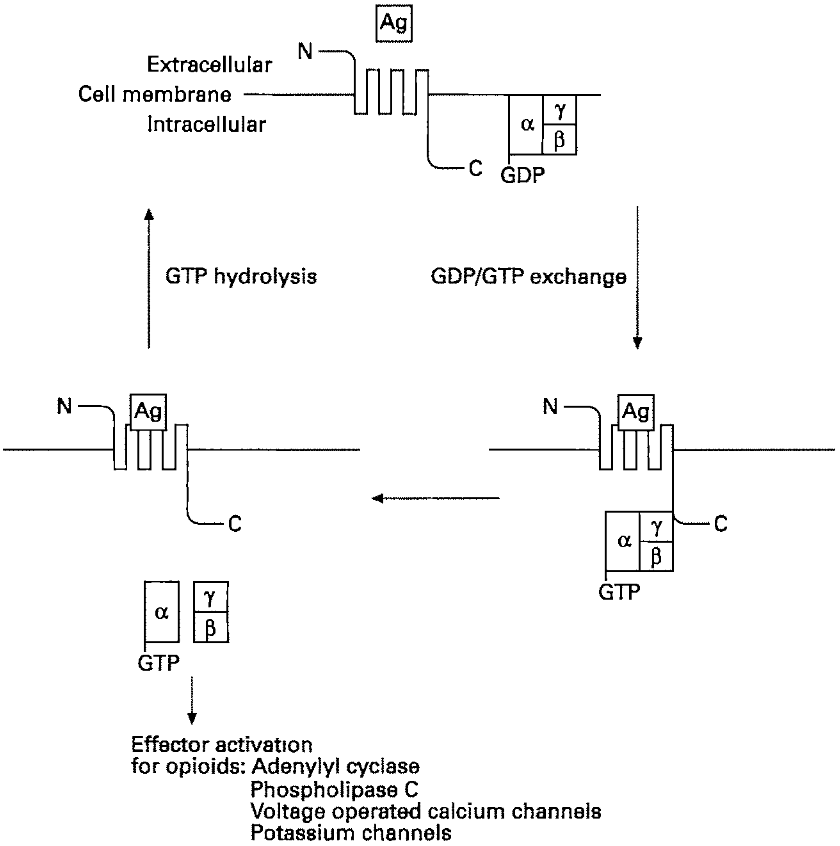

Figure 2 The G-protein cycle. (Start at the top and work clockwise.) In the absence of agonist, the G protein α subunit has guanine di-phosphate (GDP) bound and all the subunits are in close association with each other. Agonist interaction with the receptor allows coupling of the receptor to the G protein. Guanine tri-phosphate (GTP) then replaces GDP in a cleft in the α subunit, causing the split of Gα and Gβγ. The α and βγ subunits are then able to interact with effectors. The α subunit displays its own intrinsic GTPase activity, and is able to hydrolyse GTP to GDP after interaction with the effector. In doing so the α subunit inactivates itself, dissociates from the effector and re-associates with the βγ subunit. Ag = agonist, for example fentanyl.

cause release of a variety of neurotransmitters from DRG neurones[9, 11] and stimulate noradrenaline release from SK-N-SH cells.[73] Indeed, opioids have been shown to increase the duration of the action potential and reduce K^+ current in DRG neurones[21, 76] and to increase neuronal firing rate.[53]

It is thought that opioid stimulation of a variety of second-messenger systems, including adenylyl cyclase activity, phosphoinositide hydrolysis and elevations in intracellular calcium, may underlie the opioid stimulation of neuronal activity, and we shall discuss this in the remainder of the present review. The physiological role of these stimulatory actions is unclear, and the subject of much debate.

Opioid stimulation of adenylyl cyclase

A stimulatory effect of opioids on adenylyl cyclase activity was first shown more than two decades ago, after chronic opioid treatment.[16, 74, 88] In the same year a stimulatory effect of morphine on adenylyl cyclase was shown in rat corpus striatum.[69] Later it was demonstrated that opioids positively regulated adenylyl cyclase activity in chick heart cells,[49] rat heart[50] and DRG neurones.[55] Some studies have found that the stimulation of adenylyl cyclase was G_s linked,[2, 21, 76] whereas in other studies it was found to occur in a PTX-sensitive ($G_{i/o}$) manner involving βγ subunit stimulation of type II adenylyl cyclase.[43, 66, 67, 90]

It has been shown that chronic opioid treatment of the μ receptor induces type V adenylyl cyclase superactivation in COS-7 cells co-transfected with the μ opioid receptor and type V adenylyl cyclase,[3] which is time dependent, reversible and may involve βγ subunits. In contrast to this, acute opioid inhibition of adenylyl cyclase in the same cell line occurs via $\alpha_{i/o}$ subunits. The same group[4] found that opioid action of adenylyl cyclase is isozyme specific. Acute activation of the μ receptor stimulates type II, IV and VII adenylyl cyclase while inhibiting the activity of types I, V, VI and VIII. Superactivation of adenylyl cyclase stimulated types I, VI and VIII. In SK-N-SH neuroblastoma cells, activation of the μ opioid receptor stimulates the formation of cAMP in a process that is calcium/calmodulin (Ca^{2+}/CaM) dependent and is secondary to the opening of voltage-sensitive calcium channels (VOCCs). The stimulatory effect is seen

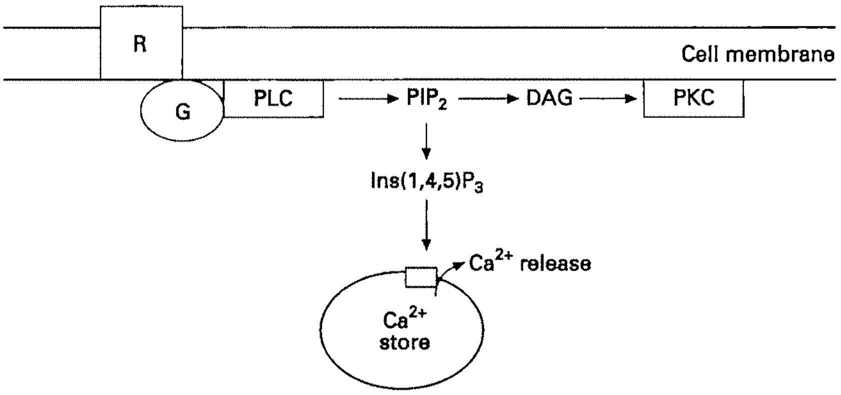

Figure 3 Simplified schematic representation of the Ins(1,4,5)P_3 cycle illustrating the link between phosphoinoside turnover and increases in $[Ca^{2+}]_i$. Receptor occupancy causes G-protein activation of PLC, which cleaves PIP_2 to yield Ins(1,4,5)P_3 and DAG. DAG activates PKC, while Ins (1,4,5)P_3 releases Ca^{2+} from intracellular stores. Ag = agonist; R = receptor; G = G protein; PIP_2 = phosphatidylinositol (4,5) bisphosphate; Ins(1,4,5)P_3 = inositol (1,4,5) trisphosphate; PLC = phospholipase C; DAG = di-acylglycerol; PKC = protein kinase C.

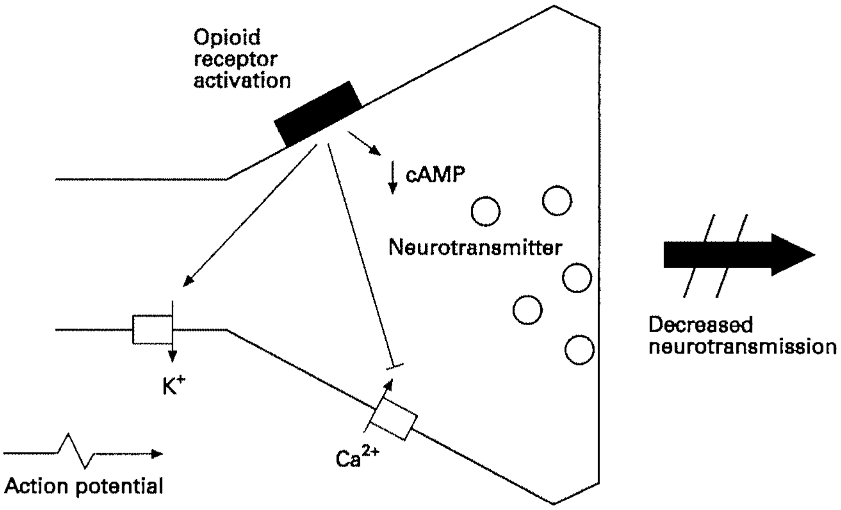

Figure 4 Presynaptic opioid receptors are thought to decrease neurotransmission *via* a reduction in cAMP levels, closure of voltage-sensitive calcium channels and activation of potassium currents. These co-ordinated changes lead to a reduction in the release of excitatory neurotransmitters and hence analgesia. After Leslie 1987.[51]

only at nM concentrations of μ agonist, whereas at higher concentrations (0. 1 μM) an inhibitory effect is seen.[51] This bimodal effect of stimulation at low concentrations of agonist and inhibition at higher doses, was also noted in myenteric plexus.[94 95] In rat olfactory bulb μ and δ opioids were shown to stimulate cAMP formation in a PTX-sensitive manner at nM and μM concentrations.[66] Stimulation of adenylyl cyclase activity also occurs in F11 neuroblastoma sensory neuron hybrid cells,[24] rat brain slices,[58] Xenopus oocytes transfected with the κ receptor[43] and human kidney cells transfected with the δ receptor.[90]

Activation of adenylyl cyclase will lead to accumulation of cAMP, which is responsible for the activation of cAMP-dependent protein kinase A. PKA activity will produce an increased level of protein phosphorylation, potentially leading to altered cellular responses. An example would be phosphorylation of synaptic proteins in nerve terminals[71] or phosphorylation of ion channels.[52] In addition, opioid activation of adenylyl cyclase leading to production of cAMP may activate the inwardly rectifying cation current I_h, the consequence of which is increased neuronal firing.[40]

Opioid stimulation of phosphoinositide hydrolysis

Activation of both recombinant and endogenous opioid receptors stimulates phosphoinositide turnover, leading to the production of Ins(1,4,5)P_3 in a variety of cell lines. In SH-SY5Y cells activation of PLC was shown to occur secondary to opening of L-type calcium channels.[83] As in all cases tested the breakdown was PTX sensitive, the role of βγ subunits released from a PTX-sensitive G protein has been addressed as a mechanism by which PLC is activated.[65 90] However it was concluded that in SH-SY5Y cells expressing endogenous μ and δ receptors, only activation of the μ receptor stimulated Ins(1,4,5)P_3 formation in a PTX-sensitive manner.[83] Also, liberation of βγ subunits from G_i by activation of δ receptors or α2 adrenoreceptors or both did not effect basal or submaximal μ-induced Ins(1,4,5)P_3 formation.[83] In these cells at least it seems that βγ subunits do not mediate PLC activation. Opioid stimulated Ins(1,4,5)P_3 formation also occurs in NG108-15 cells,[41 79 81] but the activation of PLC does not seem to be dependent upon calcium influx.[81] These differences in PLC signalling between NG108-15 cells

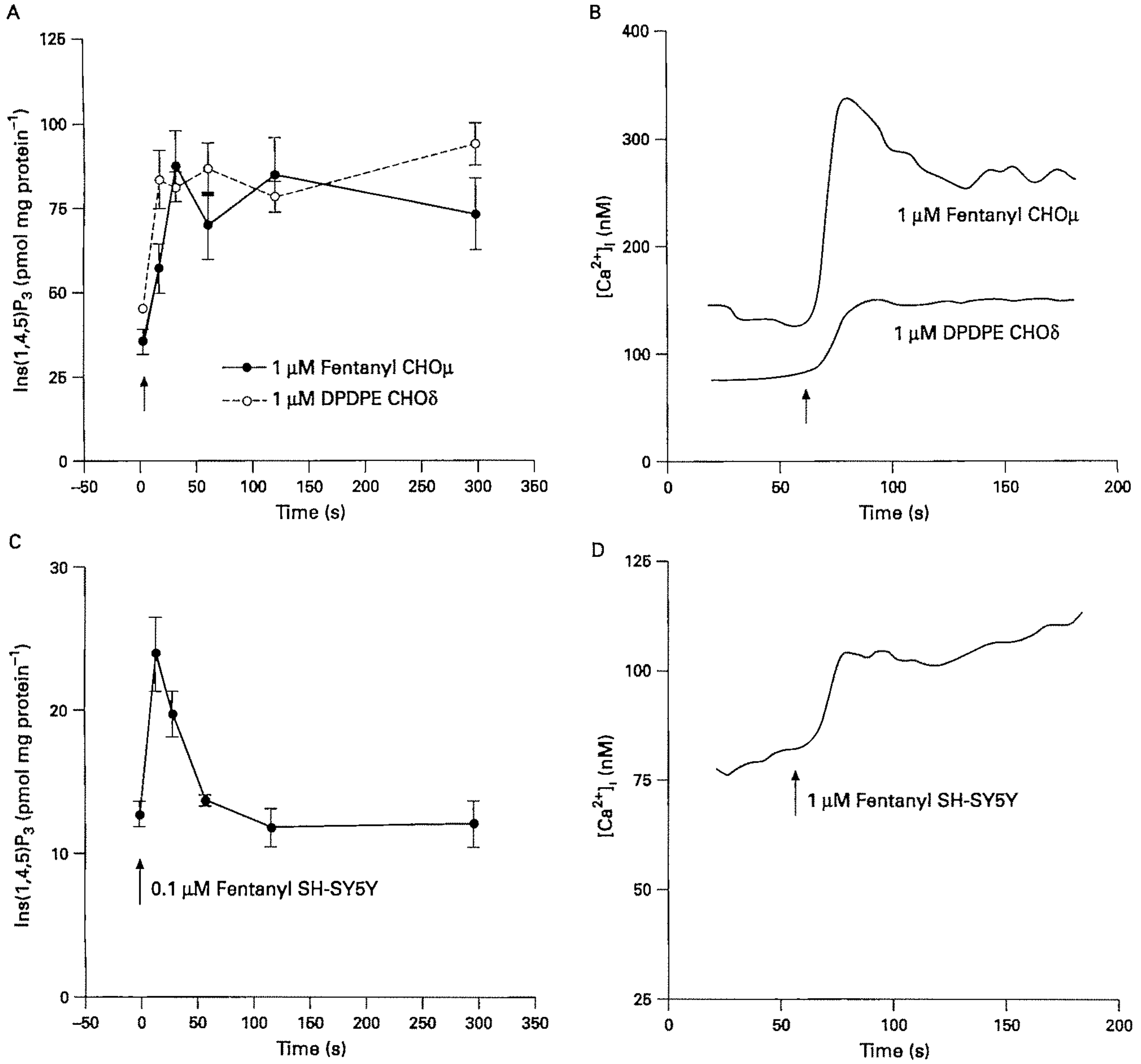

Figure 5 A) Time course of Ins(1,4,5)P_3 formation in Chinese hamster ovary (CHO) cells expressing recombinant μ and δ opioid receptors.[78 39] B) Time course of opioid-induced increases in $[Ca^{2+}]_i$ in CHO cells expressing recombinant μ and δ opioid receptors[78] (and Harrison and Lambert, unpublished observations). C) Time course of Ins(1,4,5)P_3 formation in SH-SY5Y cells [82] D) Time course of fentanyl-induced increase in $[Ca^{2+}]_i$ in SH-SY5Y cells.[93]

and SH-SY5Y cells may represent differing PLC isoforms expressed in different cell types.

Both recombinant μ and δ opioid receptors have also been shown to stimulate PLC when expressed in Chinese hamster ovary (CHO) cells,[39 78] as have transiently transfected δ receptors in human kidney cells,[90] the δ receptor expressed in Xenopus oocytes[61] and in COS-7 cells transiently expressing the μ receptor.[42] Other reports of opioid stimulation of phosphoinositide hydrolysis include rat-brain aggregates[5] and spinal cord-DRG neurones.[6] Opioid stimulation of phosphoinositide hydrolysis has been proposed as a possible mechanism for the opioid-induced release of adenosine in dorsal root ganglion neurons.[11] Examples of opioid-receptor stimulation of Ins(1,4,5)P_3 are shown in Figure 5.

Opioid stimulation of Ins(1,4,5)P_3 formation also causes concomitant activation of PKC in SH-SY5Y cells[83] and NG108-15 cells,[81] presumably via DAG formation. It has also been shown that this occurs with the δ receptor in Xenopus oocytes[91] and rat spinal trigmenial neurons.[13] The activation of PKC may lead to the phenomenon of tolerance, that is the reduced ability of opioids to produce pharmacological effects, particularly analgesia, after repeated or prolonged exposure to them. Various studies have provided evidence indicating that the stimulatory effects of opioids may be involved in the development tolerance to such drugs. The development of tolerance was prevented by blocking the stimulatory effects of opioids with etorphine or dynorphin fragments in dorsal root ganglions.[75 77] Fundytus and Coderre[32] showed that chronic inhibition of intracellular calcium release or PKC activation significantly reduced the development of morphine tolerance in rats. G-protein-coupled receptors contain PKC phosphorylation sites on the third intracellular loop and on the C terminus. Indeed it is known that the C terminus of the δ-opioid receptor is required for agonist-mediated phosphorylation.[101] Phosphorylation of these sites may cause receptor–G protein uncoupling, resulting in reduced efficacy of an opioid. Various studies have shown that potential phosphorylation sites on the C terminus are important in desensitization and down-regulation of opioid receptors,[12 25 68 89] which may be involved in the development of tolerance. Acute application of opioids to δ receptors lacking C-terminal amino acids (that is, loss of PKC phosphorylation sites) converts a sustained Ins(1,4,5)P_3 response to a monophasic response when such receptors are expressed in CHO cells.[39] Therefore the C-terminus of the δ receptor appears to be important in acute PLC coupling. In contrast to this, another study[102] found that the C-terminus of the δ-opioid receptor may not be important in agonist-mediated activation. PKC activation was shown to trigger the onset of stimulatory effects to opioids on electrically induced cAMP formation, as seen in tolerant tissue.[97] Other studies have illustrated that increased PKC activity leads to the development of tolerance,[56 57 63] through various mechanisms. Opioid-induced increases in PKC activity have been shown to modulate K^+ channels; µ-opioid-induced activation of PKC in SH-SY5Y cells may inhibit Ca^{2+}-activated K^+ channels,[83] which would prevent hyperpolarization, while in Xenopus oocytes transfected with the µ receptor, PKC activity causes desensitization of inwardly rectifying K^+ channels,[59] although this is controversial.[47] In addition to the possible role of PKC in the development of opioid tolerance (for a review, see Smart and Lambert 1996[80]), other mechanisms cannot be excluded. There is evidence that bimodal actions of opioids maybe of importance in this phenomenon, as discussed later.

Opioid induced increases in intracellular calcium

Calcium ions are one of the most ubiquitous signal transduction elements, and regulate a range of diverse cellular functions from neurotransmission to cell proliferation.[8] An intracellular calcium concentration of ~100 nM compared with an extracellular concentration of ~2. 5 mM provides a concentration gradient to make calcium ions an ideal second messenger. The cell is able to use both intra- and extracellular calcium as a signalling molecule.[15] Extracellular calcium can enter the cell through numerous types of calcium channels, such as voltage-operated calcium channels that allow calcium influx after depolarization. Intracellular calcium is released from stores within the cell after agonist stimulation as described earlier.

Opioid-induced increases in intracellular calcium may come from intracellular or extracellular sources or both. In NG108-15 cells there is a close temporal and dose–response relationship between Ins(1,4,5)P_3 formation and increases in $[Ca^{2+}]_i$, suggesting that the induced increase in Ins(1,4,5)P_3 formation is sufficient to cause a mobilization of intracellular calcium,[81] and in the same cell line inhibition of PLC blocks the increase in $[Ca^{2+}]_i$.[41] Smart and colleagues[83] found that in SH-SY5Y cells µ opioids allow calcium influx to stimulate PLC activity, resulting in Ins(1,4,5)P_3 formation, and µ opioid receptor activation in the same cells causes a modest increase in $[Ca^{2+}]_i$,[93] which may be attributable to calcium entry. The EC_{50} values obtained in the studies above for increases in $[Ca^{2+}]_i$ were much greater than for Ins(1,4,5)P_3 formation. This prompted the hypothesis that that localized increases in $[Ca^{2+}]_i$ in the vicinity of the plasma membrane may activate PLC, but these would be too small to be detected measuring $[Ca^{2+}]_i$ in whole-cell suspensions. However, another study found that synergism with other agents was necessary to produce an opioid-mediated response in SH-SY5Y cells.[17 18] Elevation of intracellular calcium by δ and µ receptors occurred only when there was ongoing muscarinic receptor activation, although the nature of the link between muscarinic occupancy and opioid mobilization of $[Ca^{2+}]_i$ was not clear. "Priming" of PLC, this time with bradykinin, was also necessary in a study carried out by Okajima and colleagues[65] in NG108-15 cells. It remains unclear why there is a discrepancy between the results of the studies using SH-SY5Y cells; it may be that differing cell culture techniques cause some cell lines to lack certain types of VOCCs.[17] Factors increasing the stimulatory effects of opioids on intracellular calcium in NG108-15 and SK-N-SH cells have been studied by Sarne and Gafni,[72] who concluded that synchronization of the cell cultures, differentiation of the cells and synergism with other stimulatory agents increased the probability and the amplitude of the response to the opioid agonist. Of these, synchronization had the most pronounced effect, possibly by producing a more homogenous cell population, and might explain the differences between the SH-SY5Y cell studies described above. Endogenous δ-opioid receptors in undifferentiated NG108-15 cells can cause release of intracellular calcium from thapsigargin-sensitive sores in a PTX-sensitive manner.[41] When expressed in CHO cells, the recombinant δ receptor couples to PLC[39] and causes an increase in $[Ca^{2+}]_i$,[35] as does the µ receptor.[78] In Xenopus oocytes the κ receptor causes mobilization of intracellular calcium,[43] as it does when expressed in CHO cells (Harrison and Lambert, unpublished observation). There is evidence to suggest that there may be interaction between the Ins(1,4,5)P_3-Ca^{2+} and the adenylyl cyclase–cAMP signalling systems in rat heart, as blockade of increases in $[Ca^{2+}]_i$ induced by κ opioid receptors also results in suppression of cAMP accumulation.[100]

As well as opioid mobilization of intracellular calcium from Ins(1,4,5)P_3-sensitive stores, there has been a report to suggest that the δ opioid receptor can regulate the activity of ryanodine receptors on intracellular calcium stores in SK-N-BE cells.[1] Like Ins(1,4,5)P_3 receptors, ryanodine receptors are calcium-release channels located on intracellular calcium stores. Cyclic adenosine diphosphate (cADP) ribose, synthesized from ATP, may be the endogenous trigger for calcium release.[7] In this report the mobilization of $[Ca^{2+}]_i$ occurred only at µM concentration of agonist, was independent of extracellular calcium and did not follow a biphasic or monophasic pattern typical of increases in $[Ca^{2+}]_i$ seen in other studies. The response was neither CTX- nor PTX-sensitive. It was suggested that there could be direct coupling between the δ receptor and the ryanodine receptor on the endoplasmic reticulum, or the δ receptor could stimulate the generation of cADP ribose.[1] Mobilization of calcium from ryanodine-sensitive stores in rat myocytes has also been observed.[85]

Table 1 Comparison of μ, δ and κ opioid receptor coupling to adenylyl cyclase $Ins(1,4,5)P_3$-$[Ca^{2+}]_i$

	Recombinant receptors		Endogenous receptors		
	CHOμ Fentanyl	CHOδ DPDPE	CHOκ Spiradoline	SH-SY5Y(μ) Fentanyl	NG108-15(δ) DPDPE
IC_{50} cAMP	38 nM	2 nM	2 nM	27 nM	1 nM
EC_{50} $Ins(1,4,5)P_3$	11 nM	55 nM	ND	16 nM	3 nM
Increased Ca^{2+}	✓	✓	✓	✓ (730nM)	✓ (3nM)

Refs. 38, 39, 48, 78, 81, 82, 93

Table 2 Adapted from Sarne and colleagues 1996[71]. Conditions required to bring about bimodality of opioid action, with selected references

Conditions required to produce bimodal effects	Selected references
Low *vs* high concentrations of opioid	Fields and Sarne 1997[31] Crain and Shen 1990[21]
Acute *vs* chronic opioid administration	Crain and Shen 1992[22] Avidor-Reiss and others 1996[3]
Change in experimental conditions	Sarne and Gafni 1996[72] Olianas and Onali 1994[67]

The physiological consequences of opioid-induced mobilization of intracellular calcium remain unclear. In one study it was shown that the rise in $[Ca^{2+}]_i$ was insufficient to cause a release of noradrenaline.[83] It may be that release of intracellular calcium activates a calcium-sensitive isoform of PKC or augments increases in intracellular calcium from other sources.

Opioids can cause increases in intracellular calcium by stimulating calcium influx into the cell. Morphine was shown to stimulate the Ca^{2+} component of the action potential[37] and to activate calcium channels.[54] Moreover, opioids were shown to increase the Ca^{2+} spike of the action potential in dorsal root ganglion neurons.[23] The increase in intracellular calcium is dependent upon extracellular calcium in several cases. For example, κ opioids,[28 84 85] δ opioids[41 86] and μ opioids[82 83 93] have been reported to cause calcium influx in a variety of cell types and uptake of $^{45}Ca^{2+}$ has been reported in neuronal cell lines.[30]

Sarne and colleagues[73] showed that concentrations of μ opioids that cause calcium influx also released norepinephrine in SK-N-SH neuroblastoma cells. The same group also showed that dopamine release was potentiated by the modulation of N-type VOCCs by μ and δ opioids.[44] This effect did not involve PTX-sensitive G proteins and was reversed to an inhibitory effect upon blockade of the channels with omega-conotoxin. Other studies have provided evidence that L-type calcium channels may be involved in the opioid-induced increase in $[Ca^{2+}]_i$.[28 79 83 86] Opioid-induced increases in intracellular calcium resulting from calcium entry may therefore be sufficient to produce neurotransmitter release, but clearly further work is need to clarify this.

A comparison of μ, δ and κ opioid-receptor coupling to adenylyl cyclase and $Ins(1,4,5)P_3$-$[Ca^{2+}]_i$ is shown in table 1. Typical increases in $Ins(1,4,5)P_3$ and $[Ca^{2+}]_i$ are shown in fig. 5.

Nociceptin/orphanin FQ

In addition to the classical opioid receptors (μ, δ and κ), cloning studies have revealed an atypical opioid receptor with 50% homology to μ, δ and κ opioid receptors, termed ORL(opioid-receptor-like)-1.[62 98] This receptor does not bind conventional opioid ligands but is found in the CNS in areas involved in pain perception, although there is debate about the overall role of its ligand in the production of analgesia or hyperalgesia.[36] An endogenous ligand, nociceptin or orphanin FQ, has been isolated.[60 70] Most reports to date indicate that nociceptin has inhibitory actions at a cellular level, although in SH-SY5Y cells, nociceptin increases intracellular calcium concentrations in the presence of carbachol.[19] In addition, in guinea pig myenteric plexus low (nM) concentrations of nociceptin enhance enkephalin release in the presence of opioid receptor blockade.[34]

Bimodal actions of opioids and their possible role in tolerance

In some cases (but not all) both inhibitory and stimulatory effects of opioids have been observed. In most, this could be for one of three reasons (table 2): low *vs* high concentrations of opioid agonist; acute *vs* chronic administration of agonist; and a change in experimental conditions.[11]

LOW VS HIGH CONCENTRATIONS OF OPIOID AGONIST

In DRG neurones, for example, neuronal stimulation[21] was enhanced by nM concentrations of opioid but inhibited by μM concentrations. Stimulation of adenylyl cyclase activity in SK-N-SH cells occurred only at nM concentrations of μ agonist, and was reversed to inhibition by application of μM doses.[31]

ACUTE *VS* CHRONIC ADMINISTRATION OF AGONIST

Crain and Shen[23] showed that chronic treatment with opioids caused sensory neurones to be supersensitive to the excitatory effects of opioids. In COS-7 cells transfected with the μ receptor and type V adenylyl cyclase, prolonged treatment with agonist caused stimulation of adenylyl cyclase whereas acute administration decreased adenylyl cyclase activity.[3]

A CHANGE IN EXPERIMENTAL CONDITIONS

In NG108-15 and SK-N-SH cells, the probability and amplitude of an increase in [Ca^{2+}]$_i$ caused by opioids was increased by synchronization of the cultures, differentiation of the cells or synergism with other stimulatory agents.[72] In rat olfactory bulb, μ and δ opioids stimulate basal cAMP but inhibit stimulated cAMP formation.[67]

There is evidence to suggest that the bimodal actions of opioids may be involved in tolerance to and dependence on opioids. Wang and Gintzler[96] showed that the opioid stimulation of cAMP in opioid-naive tissue differed from that seen in tolerant tissue. In naive tissue, inhibition was G$_i$ linked, but if this pathway was inactivated by PTX treatment then facilitation occurred in a CTX-sensitive manner. However in tolerant tissue, previously inhibitory doses (micromolar) of opioid lead to facilitation of cAMP formation in a CTX-sensitive manner. By treating opioid-naive tissue with protein phosphatase inhibitors or PKC activators, opioid inhibition of cAMP formation can be reversed to facilitation, as seen in tolerant tissue.[97] In DRG neurones treated long term with opioids, low concentrations of opioids produce excitatory effects (lengthening of action potential duration) which is G$_s$ linked and produce a counter-activation of inhibitory effects.[23] It was proposed that the balance between excitatory and inhibitory effects is dependent upon the levels of the glycolipid, GM1 ganglioside, which is found on neuronal surfaces.[22] One possible explanation for bimodal effects of opioids would be separate stimulatory and inhibitory receptors, although this does not appear to be the case, as no such receptors have been found at a molecular level. It is at present unclear whether these bimodal actions of opioids may contribute to produce tolerance or are an effect of tolerance.

Conclusion

In summary, it can be seen that opioids exert a variety of stimulatory effects on signal transduction. These include stimulation of cyclic AMP formation, phosphinoside hydrolysis, and elevation of intracellular calcium, by mobilization from intracellular stores and by stimulating influx. At a cellular level these changes may underlie an opioid stimulation of neuronal activity. In addition, the stimulatory effects of opioids may play a part in the development of tolerance to opioid drugs. Studies aimed at unravelling these intricate signalling events may contribute better to our understanding of opioid action.

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The orphanin FQ system: an emerging target for the management of pain?

T. Darland and D. K. Grandy

The successful treatment of severe and chronic pain remains a primary goal of the physician and for this purpose clinicians continue to rely on extracts prepared from the opium poppy. Unfortunately morphine, the most important of the analgesic opiates, produces several undesirable side effects including respiratory depression, constipation, the development of tolerance and physical dependence. Consequently, a considerable effort has been made over the years to identify non-opiate means for controlling pain.

One of the most exciting developments in pain management came almost 20 years ago, with the demonstration that relief could be achieved by the electrical stimulation of discrete midbrain regions, in particular the periaqueductal gray and the periventricular hypothalamus.[25 49] These findings lent support to the concept that in the central nervous system there exists specific circuitry that modulates not only senses but also painful stimuli. It is generally accepted that these circuits have supraspinal and spinal components whose neurones communicate with one another via neurotransmitters, which include the biogenic amines (dopamine, norepinephrine and serotonin) and the opioid peptides (met- and leu-enkephalin, β-endorphin and dynorphin).

These neurotransmitters all directly influence neuronal physiology by first activating cell surface proteins referred to as receptors. The noncovalent interaction between a neurotransmitter, or ligand, and its cognate receptor causes a conformational change in the receptor molecule. This change constitutes a signal that can then be detected on the intracellular face of the cell by a complex of GTP binding proteins, or simply G proteins, that interact with second messenger systems to modulate enzyme activity (for example, adenylyl cyclase and protein kinase C), ion-channel conductance (potassium and calcium) and gene expression.[24]

Although excellent targets for pharmacological manipulation, the opiate receptors are difficult proteins to work with biochemically because they are typically found in low concentration and they are labile, losing their activity upon purification away from a lipid environment. Cloning of the delta opioid receptor was therefore hailed as a major breakthrough when the work was published in 1992, and resulted in a burst of molecular studies to identify and express related receptors.[15 30]

Discovery of the opioid-like orphan receptor

The use of nucleic acid probes based on the delta opioid receptor resulted in the cloning of the mu and kappa opioid receptors,[10 38] as well as a new sequence that encoded a novel putative G protein-coupled receptor.[6 9 40 61] Although the deduced amino acid sequence of this new receptor is approximately 65% identical to the three *bona fide* opioid receptors, when expressed in tissue culture cells it fails to bind opioid ligands with high affinity. Hence this receptor came to be known as the opioid-like orphan receptor.

Distribution of the orphan receptor in the rat central nervous system

Localization studies performed in the rat have revealed that the receptor's mRNA and protein are widely distributed throughout the central nervous system.[6 40 66] Supraspinally its mRNA appears to be particularly dense in the cortex, hippocampus, hypothalamus, periaqueductal gray, dorsal raphe, and locus coeruleus (figs 1F, 2B and 2D). Although the presence of the orphan receptor's mRNA in these brain regions is similar to that reported for the opioid receptor mRNAs (reviewed in reference 36), in other areas there are striking differences. The most frequently noted of these is the caudate putamen, where mRNA encoding all three opioid receptors is easily detected but the orphan receptor's mRNA does not appear to be expressed (figs 1B and 1D).

Orphan receptor mRNA is expressed throughout the length of the spinal cord (figs 3B, 3D and 3E). In the cervical segments orphan receptor mRNA is most abundant in the superficial layers of the dorsal horn corresponding to laminae I and II (substantia gelatinosa) as well as lamina X, a distribution similar to that of the opioid receptors.[36] This distribution of orphan receptor mRNA suggests that, similar to the opioid receptors, its activation at this level of the cord could modulate nociceptive processing.

The distribution of the receptor's mRNA in the cervical cord is maintained more caudally in the thoracic cord. Essentially no labelling of receptor mRNA is seen in the intermediolateral nucleus, which contains preganglionic sympathetic neurones that are primarily involved in autonomic control (reviewed in reference 18). Changes in the distribution of orphan receptor mRNA begin to appear in

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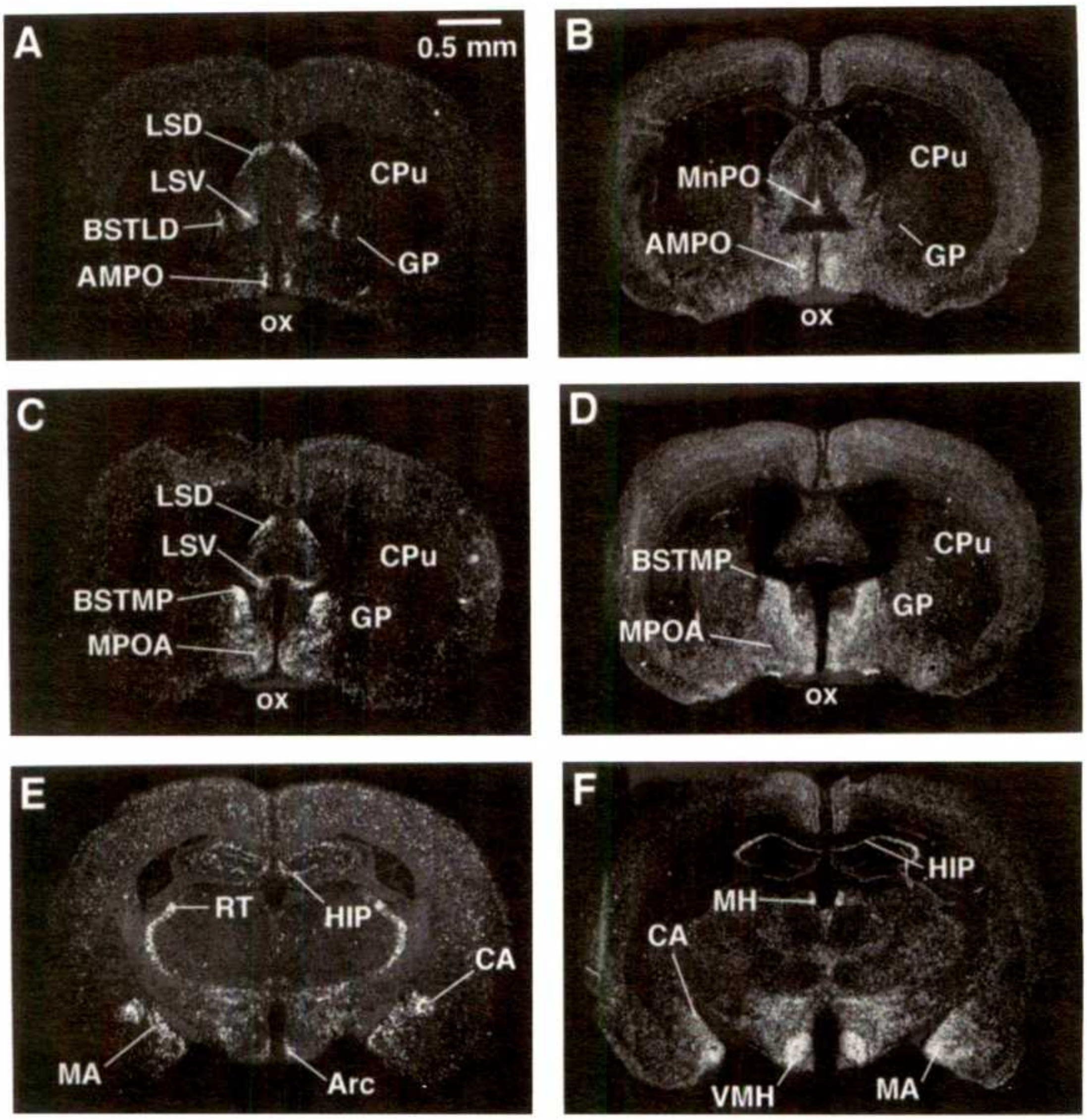

Figure 1 Distribution of prepro-orphanin FQ mRNA (A, C and E) and orphanin FQ receptor mRNA in adult rat forebrain (B, D and F). All *in-situ* hybridization was performed as described elsewhere,[12] using radiolabelled rat cDNA probes corresponding to 244 bp for prepro-OFQ and 309 bp for OFQR. Under darkfield illumination, zones of hybridization appear white. Sense probes, used as controls in these experiments, showed no detectable staining (data not shown). Arc = arcuate nucleus of the hypothalamus; AMPO = anterior medial preoptic nucleus; BSTLD = bed nucleus of stria terminalis, dorsolateral division; BSTMP = bed nucleus of stria terminalis, medial posterior division; CA = central amygdala; CPu = caudate putamen; GP = globus pallidus; HIP = hippocampus; LSD = dorsolateral septal nucleus; LSV = ventrolateral septum; MA = medial amygdala; MH = medial habenula; MnPO = median preoptic nucleus; MPOA = medial preoptic area; ox = optic chiasm; RT = reticular thalamic nucleus; VMH = ventral medial hypothalamus.

segments of the lumbar cord where, in addition to labelling the superficial layers of the dorsal horn, a significant amount of receptor mRNA is scattered throughout lamina VII of the ventral horn (fig. 3F). Some of these neurones project to the cerebellum, whereas others project to the brainstem reticular formation and to the thalamus.[28 29 64] On the sole basis of anatomical considerations it seems likely that the activation of orphan receptors expressed in these neurones could influence somatomotor processing, including nociception.

Discovery of the endogenous ligand for the opioid-like orphan receptor

Confronted with the challenge of identifying the orphan receptor's endogenous ligand, Reinscheid and colleagues[48] sought clues in the structure of the receptor and the anatomical distribution of its mRNA. On the basis of the deduced amino acid sequence of the orphan receptor's putative extracellular domains, it was predicted that the endogenous ligand would be a positively charged peptide similar in mass and charge to dynorphin. Furthermore, as the receptor's putative intracellular domains are extensively homologous with those of the opioid receptors, this suggested that when activated, the orphan receptor would also couple to the inhibition of cAMP production.

The next step was to identify a brain region from which to extract and purify the orphan receptor's endogenous ligand. For this the receptor *in-situ* hybridization data proved invaluable. The two areas where the orphan receptor mRNA is most discretely and densely expressed in brain are the hypothalamus and the locus coeruleus. Reinscheid and colleagues chose the hypothalamus as their starting material because of its size and connectivity. Meunier and

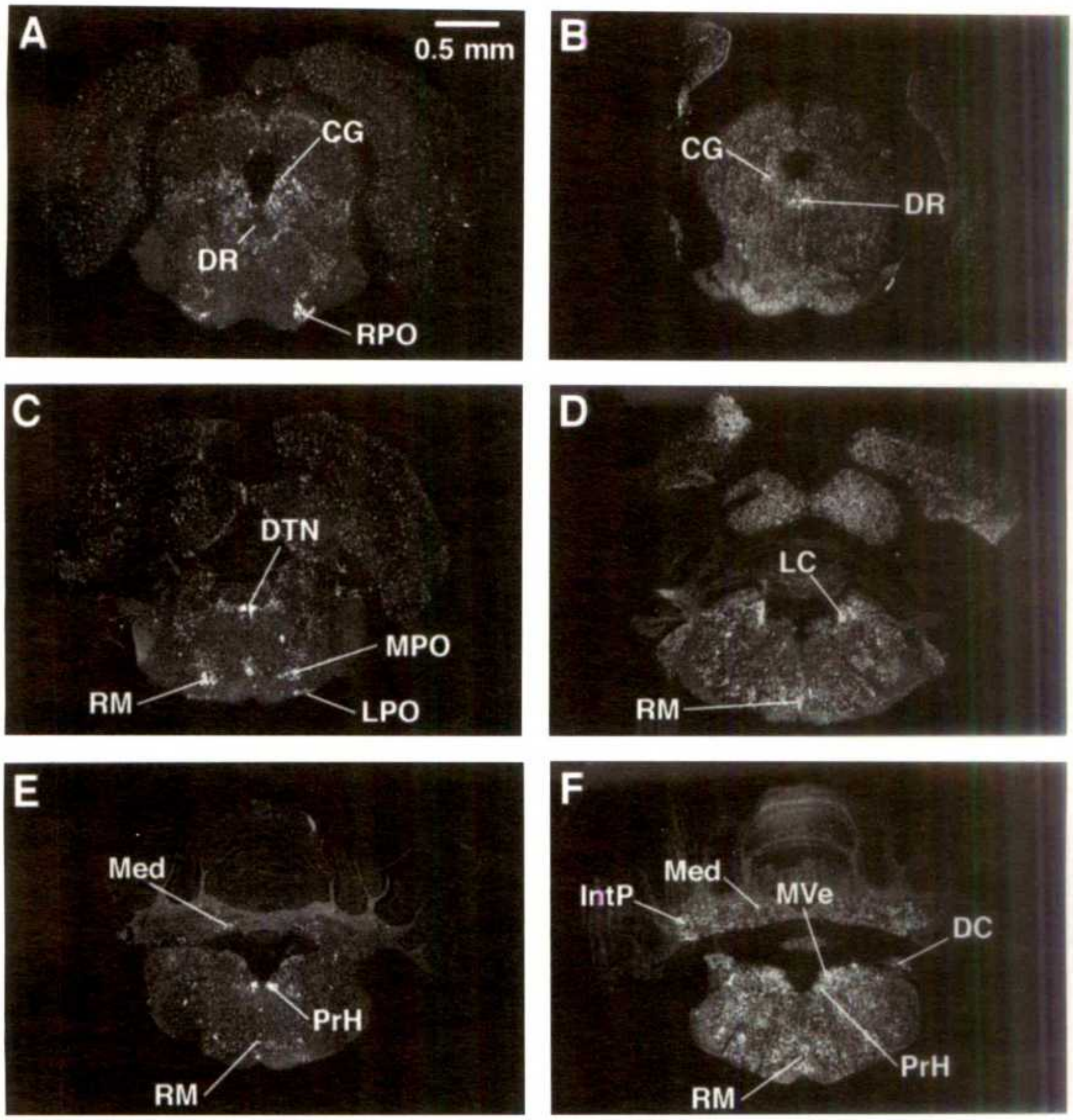

Figure 2 Distribution of prepro-orphanin FQ mRNA (A, C and E) and orphanin FQ receptor mRNA in the adult rat mesencephalon, pons, and brainstem, as determined by *in-situ* hybridization. CG = central gray; DC = dorsal cochlear nucleus; DR = dorsal raphe; DTN = dorsal tegmental nucleus; IntP = interposed cerebellar nucleus; LC = locus coeruleus; LPO = lateral periolivary nucleus; Med = medial cerebellar nucleus; MPO = medial periolivary nucleus; MVe = medial vestibular; PrH = prepositus hypoglossi; RM = raphe magnus; RPO = rostral periolivary nucleus.

colleagues[37] successfully purified the identical peptide from the extract of 20 rat brains.

After ultrafiltration and chromatography of porcine hypothalamic extracts, the resulting fractions were evaluated for their ability to activate the orphan receptor in an *in vitro* bioassay. For this purpose two Chinese hamster ovary (CHO) cell lines were used: one that stably expresses the orphan receptor and one that does not. To evaluate a particular fraction of extract both cell lines would be treated with the fraction along with forskolin, an agent that stimulates the production of cAMP. Those fractions that inhibited the forskolin-stimulated production of cAMP in cells expressing the receptor, but failed to inhibit cAMP production in the cells lacking receptor, were collected and subjected to reversed-phase high-performance liquid chromatography. Bioassay of these fractions identified a single peak of activity. The microsequence of this heptadecapeptide peptide is: Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln — a sequence that is strikingly similar to that of dynorphin.[19] To confirm that bioactivity resided in this sequence a synthetic peptide was prepared. The synthetic peptide potently and dose-dependently inhibited cAMP production in only those CHO cells expressing the orphan receptor. When used in pharmacological studies the peptide demonstrated normal binding kinetics to its cognate receptor and little cross-reactivity with the mu, delta or kappa opioid receptors. Reinscheid and colleagues named this peptide orphanin FQ-orphanin because its receptor had been known as the orphan receptor; FQ represents the N-terminal (phenylalanine, abbreviated F) and C-terminal (glutamine, abbreviated Q) residues of the peptide. Meunier and colleagues refer to the identical peptide they purified from rat brain as nociceptin.

Orphanin FQ is contained within a precursor protein

The structural similarity between OFQ and the opioid peptide dynorphin suggested that OFQ may also be synthesized as part of a precursor molecule that is subsequently processed. Efforts to identify a polypeptide that contained OFQ eventually led to the cloning of a cDNA prepared from rat brain mRNA that encodes a protein of 181 amino acids.[41 45] Orphanin's 17 amino acids are flanked by pairs of basic amino acids, known target sequences for subtilisin-like endopeptidases.[52] In the literature this precursor protein is referred to as both prepro-orphanin FQ (ppOFQ) and prepro-nociceptin.

The ppOFQ contains several peptides, in addition to OFQ, that are flanked by dibasic cleavage sites, an organization that is similar to that of prepro-dynorphin and pro-opiomelanocortin. Coincidentally, the peptide immediately following the C-terminal, dibasic amino acids of orphanin FQ, is another 17-amino-acid peptide that could also be correctly referred to as "orphanin FQ". If this peptide is found to have biological activity, it may become necessary to discriminate between the two, referring to OFQ/nociceptin as the alpha form and the other peptide as beta-OFQ/nociceptin.

The complex organization of prepro-OFQ suggests that the co-ordinated expression of OFQ and the other potentially bioactive peptides contained within it has conferred a selective survival advantage on the organism. Determining the functions that these potential prepro-OFQ progeny serve *in vivo* is currently an area of great interest.

Expression of prepro-orphanin FQ in the rat central nervous system

In addition to revealing that OFQ is processed from a precursor polypeptide, the cloning of the rat ppOFQ cDNA has provided valuable *in-situ* hybridization probes. With these, the detailed mapping of ppOFQ expression throughout the central nervous system has begun in an effort to better understand the peptide's functions in the central nervous system.[26 41 45 66]

THE TELENCEPHALON

Of the relatively little ppOFQ mRNA expressed in the rat cerebral cortex, the density of hybridization is greater in the superficial rather than deeper layers (fig. 1E). This expression pattern appears to be uniform along the rostral-caudal axis of the cortex. In this context, it is worth noting that OFQ has been reported to decrease glutamate release within cerebrocortical slices.[43]

In the medial and central divisions of the amygdala, the lateral ventral and lateral dorsal septal nuclei, the anterior and medial posterior divisions of the bed nucleus of the stria terminalis (BST) and the medial preoptic area (POA), the expression of ppOFQ mRNA is dense (fig1). The amygdala and POA have reciprocal connections with the BST, as do the ventral tegmental area, locus coeruleus, dorsal raphe and raphe magnus. On the basis of these findings one role of OFQ, or the other peptides processed from ppOFQ, or both, may be to regulate and co-ordinate the firing of the major monoaminergic nuclei, thereby linking vigilance with the emotional and motivational states of the animal. It may prove informative to explore the possibility that OFQ circuits involving the BST may have some bearing on opiate dependence and withdrawal.

The POA, BST and amygdala are sexually dimorphic areas and as such are subject to regulation by sex hormones (reviewed in reference 51). The finding that both the ppOFQ and receptor mRNAs are intensely expressed in these areas (figs 1A and 1C) suggests a possible role for the OFQ system in the expression of sexually dimorphic behavioural responses, including perhaps responsiveness to opiates. It has also been recently reported that OFQ stimulates lordosis in female rats (reviewed in reference 67).

In the hippocampus ppOFQ probes produced moderate labelling of CA1, CA2 and CA3 hippocampal neurones but the signal was considerably weaker in neurones of the dentate gyrus (fig. 1E). This expression pattern suggests a role for the OFQ system in learning and memory, and rats have been reported to have impaired spatial learning in the Morris water task, without decreased swimming performance, after injection of OFQ into the CA3 region of the dorsal hippocampus.[50]

In the rat striatum, a ppOFQ probe lightly labelled the ventral pallidum and globus pallidus while, similar to the receptor, the caudate putamen and nucleus accumbens were conspicuously devoid of ppOFQ mRNA (figs 1A and 1C).

THE DIENCEPHALON

The expression of ppOFQ mRNA is dense in several structures of the diencephalon, including the subparafascicular (data not shown) and reticular thalamic nucleus (RT, fig. 1E). The RT is interesting because it has reciprocal connections with most, if not all, of the other thalamic nuclei, and is responsible for a rhythmic modulation of corticothalamic neuronal electrical activity, which has been found to be correlated with the animal's level of vigilance.[54] The output of the RT is inhibitory and most of its neurones, at least in rat, are GABAergic. Therefore, future studies might usefully explore the effect of OFQ on the discharge rates of RT neurones and cortical electroencephalogram activity during somnolence and waking states.

Other thalamic nuclei expressing ppOFQ mRNA include the paratenial and central medial nuclei, which were moderately labelled (our unpublished results). The ventral lateral geniculate and intergeniculate leaflet displayed moderate staining while the dorsal lateral and medial geniculate appeared to be negative for ppOFQ (our unpublished results) as were the habenula, the ventrolateral, ventromedial and paraventricular thalamic nuclei (fig. 1E).

In the hypothalamus, dense expression of ppOFQ was detected in the arcuate nucleus, the zona incerta and anterior hypothalamic area (figs 1C and 1E, and unpublished results). Moderate expression was detected in the paraventricular nucleus, the dorsomedial nucleus and the lateral hypothalamic area. Conspicuously lacking ppOFQ mRNA were the ventral medial nucleus of the hypothalamus (VMH) (fig. 1E), the suprachiasmatic and supraoptic nuclei (data not shown). The mammillary nuclei and the pituitary were also negative with respect to detectable ppOFQ expression (data not shown).

The relatively high level of OFQ receptor mRNA detected in the hypothalamus by *in-situ* hybridization figured importantly in the successful purification of OFQ.[48] Indeed, as measured by a recently developed radioimmunoassay, the concentration of OFQ peptide is highest in the rat hypothalamus.[47] This correlates well with the heavy expression of OFQ receptor mRNA in the arcuate nucleus, VMH and the paraventricular nucleus.

As the VMH is thought to be involved in reproductive behaviour it is possible that OFQ originating in other sexually important areas such as the BST may participate in regulating output from the VMH. The VMH is also recognized as an important area that may regulate feeding behaviour, a hypothesis that has received support from the demonstration that OFQ injected into the VMH stimulated feeding in sated rats.[46 55]

The paraventricular nucleus of the hypothalamus is an important source of corticotropin-releasing hormone, which is involved in the regulation of the hypothalamic–pituitary–adrenocortical (HPA) stress axis.[20] Afferents to the paraventricular nucleus include those originating in the lateral septum, the BST and the POA (reviewed in reference 23). These areas are thought to be involved in the production of fear and anxiety, and given that ppOFQ mRNA is heavily expressed in these projecting areas this peptide may well be a new modulator of the HPA axis.

The abundant expression of ppOFQ mRNA in the arcuate nucleus raises several interesting possibilities, given the complex nature of its connections. It has been demonstrated by Wagner et al[60] that OFQ receptors are functional in GnRH-positive neurones of the arcuate nucleus, suggesting that OFQ may modulate the pulsatile release of this important reproductive hormone. Wagner and colleagues have also demonstrated the presence of functional OFQ receptors on tyrosine-hydroxylase-positive and β-endorphin-positive neurones in the arcuate nucleus. Therefore, it is likely that OFQ affects dopamine neurones that influence the pituitary and ultimately prolactin secretion as well as opioid neurones that project throughout the brain.

THE MESENCEPHALON

In the midbrain ppOFQ mRNA is densely to moderately expressed in the periaqueductal grey (PAG) and moderately expressed in the superficial gray layer of the superior colliculus, whereas all layers of the inferior colliculus were lightly labelled (fig. 2A), as was the ventral tegmental area and substantia nigra pars compacta (data not shown). No ppOFQ expression was detected in the interpeduncular nuclei, the substantia nigra or the red nucleus (data not shown).

In addition to its role in various behaviours, the PAG is widely recognized as an important area of the brain in terms of nociceptive processing. The basis for this is, in part, the ability of electrical stimulation of the PAG to produce analgesia in animals and relieve severe pain in humans, and the realization that opioids can produce profound analgesia when administered into the PAG.[25] Because of the complexity of the PAG it has been difficult to map out an analgesia circuit. However, much work indicates that the PAG receives innervation from the hypothalamus, forebrain and ascending nociceptors from laminae I and V of the dorsal horn.[3] Some PAG neurones project to the intralaminar nuclei of the thalamus and to the hypothalamus.[14] This innervation has important implications for the integration of painful sensations and emotional behaviour. The PAG also innervates the locus coeruleus and the raphe magnus. These areas are known to possess substantial projections to the dorsal horn of the spinal cord where they can inhibit the transmission of incoming nociceptive information within the substantia gelatinosa of the dorsal horn (reviewed in reference 2). Consequently, the dense expression of both ppOFQ and OFQ receptor mRNAs throughout the PAG suggests a role in modulating nociception, which is supported by several recently published behavioural and electrophysiological studies.

THE PONS, MEDULLA AND CEREBELLUM

The rostral periolivary region and the medioventral, lateroventral and superior periolivary nuclei in the brainstem all displayed dense expression of the ppOFQ mRNA, as did the posterodorsal tegmental nucleus and the prepositus hypoglossi (fig. 2). The raphe magnus and locus coeruleus, nucleus of the solitary tract, interpolar spinal trigeminal nucleus, lateral lemniscus, and pedunculopontine and microcellular tegmental nuclei all demonstrated moderate labelling (fig. 2, unpublished results, and references previously listed). No ppOFQ mRNA was detected in the nucleus paragigantocellularis, dorsal raphe, or pontine, vestibular or cochlear nuclei. In the cerebellum only the medial cerebellar nucleus appeared to express ppOFQ mRNA.

The dense labelling of the periolivary region by ppOFQ probes suggests that the peptide may be important in regulating the auditory system. It is notable that mice deficient in OFQ receptors have a substantially reduced ability to adapt their auditory brainstem response upon exposure to intense sound.[44] The ppOFQ mRNA-positive neurons in the periolivary region project to important relay nuclei in the auditory system, which express OFQ receptor mRNA. The most important of these are the medial vestibular nucleus and the dorsal and lateral cochlear nuclei (data not shown). It remains to be determined whether OFQ exerts its effects on the auditory system via these nuclei or perhaps by acting directly on the hair cells of the cochlea, as ppOFQ mRNA is expressed in areas where some of the neurones project directly to the outer hair cells.[5]

The locus coeruleus, the major noradrenergic nucleus in brain, displays high levels of OFQ receptor mRNA (fig. 2D) and protein.[1] A high level of expression has also been detected in the prepositus hypoglossi (fig. 2E), one of the two major afferents to the locus coeruleus. The other, nucleus paragigantocellularis, was negative for ppOFQ mRNA (data not shown). Therefore, on the sole basis of *in-situ* hybridization data, it seems likely that OFQ will be found to be a major modulator of locus coeruleus output *in vivo*. OFQ has been shown to potently hyperpolarize neurones in the locus coeruleus (see below). As the locus coeruleus is important for determining the arousal state of the animal, it is anticipated that OFQ may have sedative effects.

Expression of ppOFQ mRNA in the spinal cord

The expression pattern of ppOFQ mRNA has also been examined in the cervical, thoracic and lumbar segments of the rat spinal cord. While some diffuse signal was detected centrally in all segments exam-

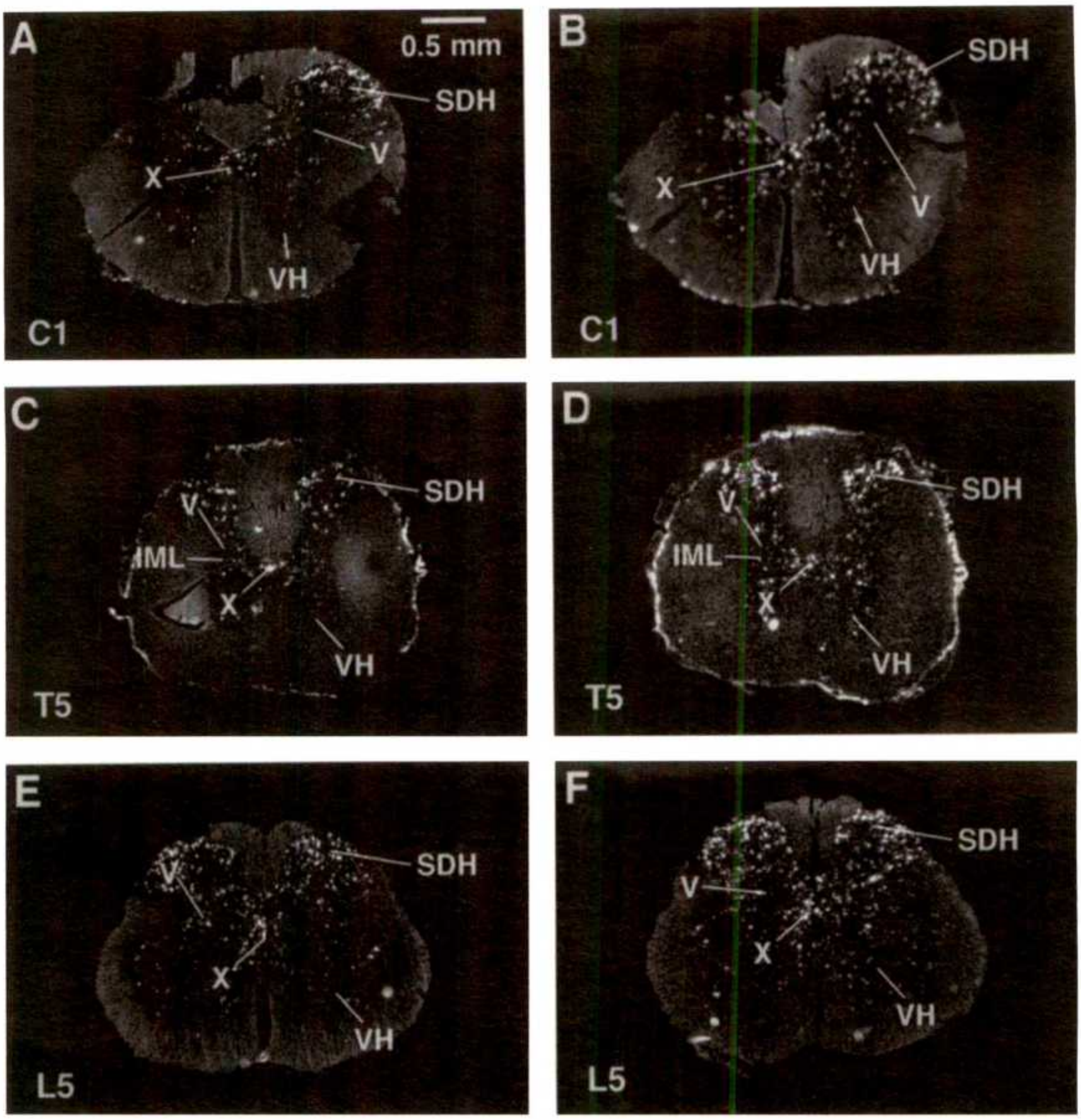

Figure 3 Distribution of prepro-orphanin FQ mRNA (A, C and E) and orphanin FQ receptor mRNA in the spinal column of the adult rat (B, D and F), as determined by *in-situ* hybridization analysis. C1 = corresponding to cervical segment 1; IML = intermediolateral nucleus; L5 = corresponding to lumbar segment 5; SDH = superficial dorsal horn equivalent to laminae I, II and III; T5 = corresponding to thoracic segment 5; V = lamina five; VH = ventral horn; X = area 10.

ined, the most intense hybridization to ppOFQ mRNA was confined to the superficial layers of the dorsal horn corresponding to laminae I and II (fig. 3). In cervical sections faint hybridization corresponding to either ppOFQ or the OFQ receptor was detected in lamina V, although some signal can be seen in lamina X. In more caudal regions of the cord hybridization to ppOFQ transcripts were seen in the superficial layers of the dorsal horn, lamina V, as well as scattered cells in lamina VII of the ventral horn (fig. 3E). Essentially no labelling was seen in the intermediolateral zone, the area in which preganglionic sympathetic efferents are concentrated.

It has been reported that the activity of superficial dorsal horn neurones is inhibited by OFQ.[16 35 53 62] Most primary nociceptive afferents terminate in laminae II and V.[8] Many neurones in these regions are nociceptive and project rostrally to the reticular formation, thalamus and other parts of the forebrain. The dense expression of ppOFQ mRNA, as well as its receptor mRNA, in areas of the dorsal horn that are known to be involved in the transmission of noxious information strongly suggests a role for the OFQ system in modulating nociceptive transmission in the cord. It is not yet known whether the spinal neurones expressing OFQ project rostrally. However, the anatomical observation that little OFQ receptor mRNA or protein are seen in the ventral basal and posterior thalamus argues against expression in spinothalamic neurones (our unpublished results and reference 1). Therefore the neurones expressing OFQ in the dorsal horn are likely to be interneurones.

Electrophysiological actions of OFQ

Among the first studies to be conducted with synthetic OFQ peptide involved electrophysiological recording from slices of rat brain. In these initial experiments locus coeruleus neurones dose-dependently responded to the peptide with a large outward current. It was later shown that this current is carried by potassium ions flowing through inwardly rectifying potassium channels, the net effect of which is hyperpolarization.[11] In addition to locus coeruleus neurones, this finding has been extended to neurones in the dorsal raphe,[58] PAG[59] and hippocampal pyramidal cells.[27] In studies involving hippocampal neurones it has been demonstrated that activated OFQ receptors also couple to calcium channels of the N1, L and P/Q type.[32] Therefore, at the level of cellular physiology, the consequences of activating the OFQ receptor are similar, if not identical, to the activation of the opioid receptors.

Actions of OFQ in algesiometric assays

Once it had been demonstrated pharmacologically and biochemically that the synthetic OFQ peptide can activate receptors that are heterologously expressed in cultured cells as well as tissue slices, the next important question became: what does it do in the whole animal? Opioids can produce analgesia by their activation of supraspinal as well as spinal receptors. As *in-situ* hybridization studies indicated that the OFQ receptor mRNA is expressed in both the brain and the spinal cord of rodents it was necessary to evaluate OFQ's actions both supraspinally and spinally. Although initial speculation favoured the possibility that OFQ would produce some degree of analgesia when administered *in vivo*, the story has proven to be more complex.

Supraspinal actions of OFQ

The fact that the OFQ peptide is rather large and positively charged at neutral pH suggests that it will not cross the blood–brain barrier easily, and as a consequence must be delivered directly into the brains of anaesthetized mice by intracerebroventricular injection (i.c.v.). In behavioural assays of nociceptive sensitivity, OFQ administered by i.c.v. has been shown to antagonize the analgesic effects of stress,[39] morphine[39,56] and electroacupuncture.[57]

The i.c.v. injection procedure is stressful enough to produce an opioid-mediated analgesia that can be detected by choosing a sensitive measure of nociception such as the abdominal constriction assay. When this assay was used by Mogil and colleagues[39] the i.c.v. injection procedure produced a quantifiable, opioid-mediated analgesia in Swiss–Webster mice that could be reversed by the opioid antagonist naloxone. Unexpectedly, in this assay OFQ failed to potentiate analgesia but rather dose-dependently reversed it.

Initial reports that OFQ produced hyperalgesia[37,48] must be viewed with caution in light of the peptide's reversal of stress-induced analgesia. It is notable that Mogil and colleagues compared the response of an animal to the noxious stimulus before any manipulation (including handling) with the animal's nociceptive sensitivity after handling, anaesthesia and i.c.v. injection of OFQ, and reported that they never saw OFQ produce hyperalgesia.

After the realization that OFQ can act as a functional antiopioid, i.e. reverse opioid-mediated stress-induced analgesia when given i.c.v., Mogil and colleagues hypothesized that the peptide might also reverse morphine-induced analgesia. When this hypothesis was tested using the tail-withdrawal and hotplate assays, OFQ (delivered by i.c.v. injection) dose-dependently reversed morphine-induced analgesia. Additional studies have demonstrated that OFQ can reverse analgesia after activation of mu, delta and kappa opioid receptors in the mouse.[39] Similar findings have also been reported in the rat.[56]

OFQ administered i.c.v. has also been shown to dose-dependently block the analgesia induced by electroacupuncture as measured in a radiant-heat tail-flick assay.[57] In addition, antisense OFQ receptor oligonucleotides potentiated analgesia by electroacupuncture, presumably by interfering with expression.

Mechanisms explaining the antagonistic effects of supraspinal OFQ on analgesia are being investigated. Although the exact brain structures responsible for these responses remain to be identified, the periaqueductal gray is an attractive candidate. The reasons for this include reports that OFQ inhibits the firing of neurones in the periaqueductal gray via both pre- and post-synaptic actions,[59] together with the observation that the peptide can have profound behavioural consequences with respect to an animal's response to morphine.[42] Another brain region that has been shown to be exquisitely sensitive to the effects of exogenous OFQ is the RVM.[22] The demonstration that OFQ potently blocks the analgesic effect of opioids when locally administered to the RVM is consistent with the peptide's ability to suppress the firing of "off-cells", a population of neurones that when disinhibited by opiates interfere with nociceptive processing in the dorsal horn of the spinal cord (reviewed in reference 17).

Spinal actions of OFQ

In contrast to its functional supraspinal, anti-opioid actions, OFQ is reported to be capable of producing analgesia when administered intrathecally (i.t.).[31,63] Using the tail-withdrawal assay as the measure of nociceptive sensitivity, Grisel and colleagues[21] demonstrated that OFQ administered i.t. in mice does not reverse morphine analgesia but rather there was a trend toward potentiating the morphine analgesia. In rats, i.t. OFQ produces significant analgesia as measured using the tail-flick assay and potentiates the analgesia produced by morphine[39,56] and electroacupuncture.[57] In addition, OFQ administered i.t. attenuated the increased nociceptive responsiveness resulting from nerve injury or inflammation.[65]

In summary, anatomical distribution, electrophysiology and behavioural studies all strongly suggest that that OFQ has a role in pain modulation and nociception. Judging by the contrasting activity of OFQ in brain and spinal cord, this role clearly involves the co-ordinated activity of multiple areas of the central nervous system.

Future directions

The expression pattern of ppOFQ and its receptor, as well as the documented functional anti-opioid effects that OFQ produces in mice and rats exposed to morphine, strongly suggest that the pharmacological manipulation of this system may have important clinical applications ranging from pain management to the treatment of tolerance and dependence. Furthermore, the sheer abundance of OFQ peptide in the brain and spinal cord implies that it is a major neurotransmitter, on a par with the opioid peptides and the biogenic amines dopamine, noradrenaline and serotonin. Consequently, a better understanding of the relationship between the OFQ system and these others will help us to comprehend the neuroanatomical and neurophysiological underpinnings of many behaviours.

If we are to expand our knowledge of the role of OFQ, we must be certain about what effects are attributable to the activation of its receptor. Therefore a selective antagonist is required before we can progress much further *in vivo*. Equipped with such a reagent it should be possible to identify those actions that are the direct consequence of OFQ receptor activation, in addition to reconciling some of the conflicting reports about the behavioural effects of OFQ. Although there has been some progress in the identification of novel ligands with high affinity for the OFQ receptor,[13] no selective antagonists have been reported. Of course the identification of new ligands involves much effort and complex screening processes. In this regard two of the classic preparations that are still used for screening purposes are the guinea pig ileum and the mouse vas deferens.[33 34] These two smooth-muscle preparations have repeatedly proven their worth in the search for novel opioid receptor antagonists, and with reports describing OFQ effects in these two preparations[4 7 68] and the establishment of cell lines that stably express the receptor, many of the necessary screening tools are available for the identification of new OFQ-receptor ligands.

More detailed anatomical mapping of the OFQ system is also needed, and this will require the development of additional immunocytochemical reagents. Retrograde tracing and stereotaxic microinjection experiments are likely to provide important information as we attempt to define further the neuronal circuitry influenced by OFQ.

Finally, transgenic mice that lack the OFQ receptor have already revealed an unexpected role for this system in hearing,[44] and will undoubtedly provide new insights into the role of the OFQ system in other behaviours. As these animals become available to more investigators we can expect a wealth of new information about the *in vivo* functions of the OFQ system to emerge. It can also be anticipated that the next generation of transgenic mice will carry inducible vectors whose activation will result in the selective disruption of a target sequence, thereby avoiding the problems of interpretation that can accompany the more traditional developmental knockouts.

We are in a period of rapid discovery with respect to this major new neurotransmitter system. One of the challenges before us is to apply our expanding basic knowledge about the OFQ system to the management of pain.

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Note added to proof

Guerrini et al recently reported an OFQ antagonist (Guerrini R, Calo G, Rizzi A, Bigoni R, Bianchi G, Salvadori S, Regoli D. A new selective anagonist of the nociceptin receptor. *British Journal of Pharmacology* 1998; 123: 163–165.)

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Recent advances and developments in the clinical use of i.v. opioids during the peroperative period

J. W. SEAR

The provision of general anaesthesia requires the administration of drugs to suppress movement in response to noxious stimuli and responses to autonomic stimulation of the sympathetic and parasympathetic nervous systems, to abolish awareness, and to relieve pain. Pain relief can be achieved by use of nitrous oxide as part of a balanced anaesthetic; by opioids or related drugs given intravenously or systemically; by other drugs having analgesic properties (for example, phencyclidines such as ketamine, or the NSAIDs); or by local anaesthetic agents, given topically by local infiltration to provide nerve or plexus blockade, or by the spinal route. In this review I shall consider the use of opioid drugs as part of balanced or other anaesthetic techniques for anaesthesia.

The analgesic properties of morphine have been known since they were described by Theophrastus in the third century BC, but there is a continuing quest for newer and pharmacologically purer drugs that bring about analgesia without the unwanted other effects of the opium alkaloids. The first such synthetic agent was pethidine, produced in 1938; its use as part of a balanced technique using nitrous oxide was described by Neff and colleagues.[84] In 1958 Bailey and colleagues used pethidine with oxygen for cardiac surgery.[8] This led in turn to reports of the cardiovascular stability observed when large doses of morphine (0.5–1.0 mg kg^{-1}) were given to patients with compromised cardiovascular function.[74] However, the technique was not without its problems, namely intraoperative recall, failure to prevent intraoperative hypertension, histamine-related hypotension and increased perioperative fluid requirements. In an attempt to remedy these side effects, some clinicians used even larger doses of morphine (up to 10 mg kg^{-1}), although this was found to be associated with greater haemodynamic instability.[120] Other side-effects included the potential for addiction and pronounced respiratory depression.

In the course of the evaluation of alternative drugs with a greater analgesic selectivity, nalorphine was synthesized. Nalorphine not only reversed the respiratory depressant effects of morphine but also had intrinsic analgesic properties. This led to the development of other drugs showing mixed agonist and antagonist activities (such as pentazocine, butorphanol and buprenorphine), and the concept that there was more than one type of opiate receptor.[78]

The introduction of fentanyl and development of the various newer congeners (especially alfentanil and sufentanil, and more recently remifentanil) has allowed the clinician to use drugs with analgesic and other properties similar to those of morphine and pethidine, but with greater potency, inactive metabolites and fewer side effects — particularly those relating to histamine release.

Newer synthetic opioids in clinical practice

FENTANYL

Fentanyl, the first of the present generation of potent anilino-piperidine opioids, was introduced into clinical practice in the mid-1960s. It was shown to be 100–300 times as potent as morphine, with a high therapeutic index, and fewer adverse side effects. In combination with nitrous oxide or with major tranquillizers such as droperidol, fentanyl produced analgesia, amnesia, an absence of obvious motor activity, depression of autonomic reflexes and, importantly, cardiovascular stability.

The opioid was often administered as an initial bolus dose of 0.2–0.3 mg with supplements of 0.1 mg[85] or by a continuous infusion.[3 51 77] One problem with fentanyl was the wide inter-individual variability, as typified in the paper of Reilly and colleagues, who described a wide range of variability in disposition (when expressed as plasma concentration–time data) within seven different sets of parameters.[100]

In the 1990s, the optimal strategy for dosing with fentanyl is probably that of "balanced anaesthesia", where fentanyl is supplemented by isoflurane or another volatile agent. To provide analgesia, plasma drug concentrations need to be around 1–2 ng ml^{-1}; this can best be achieved using a loading dose of 2–8 μg kg^{-1} and an infusion thereafter of 0.5–3.0 μg kg^{-1} h^{-1}.

However, there is a problem with infusing fentanyl for intraoperative analgesia — this highly lipid-soluble drug is significantly liable to accumulate in lipophilic peripheral tissues, with a resulting marked increase in the "context sensitive half-time" (see later)[59] (fig. 1).

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Keywords: kidney, disease; liver, disease; pharmacodynamics, anaesthetics opioid; pharmacokinetics, anaesthetics opioid; pharmacology, anaesthetics opioid

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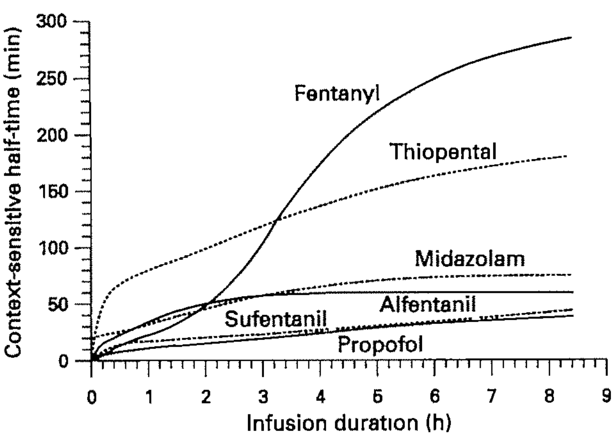

Figure 1 Context-sensitive half-times as a function of infusion duration for each of the pharmacokinetic models simulated. Solid and dashed lines are used only to permit overlapping lines to be distinguished. Adapted with permission from Hughes and colleagues.[59]

ALFENTANIL

Alfentanil shows about one-fifth the potency of fentanyl; it is shorter acting and has a faster onset-to-peak effect. There are many reports of the use of alfentanil to supplement nitrous oxide for surgery.[4 5 39 68 69 92 101 125] However, few studies have recruited sufficient participants to demonstrate the full side effects profile of the opioid, whether used alone or in combination with an hypnotic or volatile agent.

In a multicentre study from Canada, a continuous variable-rate infusion of alfentanil (0.5–1.5 µg kg^{-1} min^{-1}) was used to supplement 67% nitrous oxide and isoflurane.[98] The duration of anaesthesia averaged 117 min, with the infusion being stopped 10–15 min before the expected end of surgery. Postoperative recovery times were measured from cessation of nitrous oxide and isoflurane to opening eyes on command (6 min), response to verbal commands (8 min), and full alertness (22 min). However this apparent prompt and complete recovery from the alfentanil–isoflurane combination was at the cost of perioperative side effects: hypotension was seen in 26.2%, hypertension in 20.6%, bradycardia in 14.9% and tachycardia in 12.1%. Other side effects included muscular rigidity (8.4%), nausea (13.1%) and vomiting (4.7%). However, many of these effects were considered not to be attributable to the alfentanil; and overall satisfaction with the conduct of anaesthesia was more than 98%.

SUFENTANIL

In contrast to fentanyl, sufentanil is 7–10 times more potent than the parent drug. It has a higher affinity for stereospecific receptor-binding sites, and shows minimal binding to nonspecific sites. There is, however, a slower dissociation rate from the µ receptor.[72] When used in balanced anaesthesia or as a sole agent sufentanil is more effective than fentanyl, for reasons that are somewhat unclear. The agents have similar onset times but the duration of sufentanil is shorter, especially when the drug is given by multiple dosing or continuous infusion.[115] Its elimination half-life (140–200 min) is shorter than that of fentanyl (150–400 min).

When given in doses of 10–25 µg kg^{-1} as a sole agent for cardiac and major vascular anaesthesia, sufentanil was associated with evidence of improved outcome.[12] However, Philbin and colleagues were unable to define plasma concentrations associated with no response to intubation and sternotomy.[94] There is some suggestion that in cardiac surgical patients sufentanil provides better intraoperative stability than fentanyl, in terms of decreased hypertension and tachycardia, and hence reduced myocardial oxygen consumption, and shorter postoperative respiratory depression.[31]

REMIFENTANIL

At the time of writing (October 1997) there are few published data on the clinical use of remifentanil in comparative studies with other analgesic drugs. However, in a recently published comparison with alfentanil (1.0 µg kg^{-1} min^{-1}), infusions of remifentanil (0.5 µg kg^{-1} min^{-1}) were given to supplement 67% nitrous oxide and 0.4% isoflurane in patients undergoing lower abdominal surgery.[105] The infusion rates were halved after intubation, and bolus doses given or the infusion rates changed if there were positive responses to surgical stimuli.

In the remifentanil group, fewer patients responded to intubation and incision, and during surgery. At the end of the operation, recovery to extubation was marginally faster in the remifentanil group, but there were no differences in times to onset of spontaneous ventilation, response to verbal command and discharge from the recovery room. Comparing the side effect profiles of the two drugs, the overall incidence was similar in the two groups; but the remifentanil group showed a higher intraoperative incidence of bradycardia and hypotension. The remifentanil infusion was continued after operation in that arm of the study, but was associated with reports of postoperative apnoea and muscular rigidity. It is difficut to draw overall conclusions from the study, because it appears that non-equipotent doses of the two drugs may have been used during operation and the postoperative infusion of remifentanil would seem to require intensive supervision of the patients on a one-to-one basis to detect apnoea and respiratory depression, which may be impractical with the routine staffing levels of most recovery units.

Two other areas of interest relate to use of the opioid during neurosurgical and cardiac anaesthesia. Guy and colleagues have compared remifentanil and fentanyl during anaesthesia in patients undergoing supratentorial craniotomy.[49] The opioids were given by infusion to supplement 67% nitrous oxide (1 and 2 µg kg^{-1} min^{-1}, reducing to 0.03 and 0.2 µg kg^{-1} min^{-1} respectively). Additional boluses of 1 and 2 µg kg^{-1} of remifentanil and fentanyl were given, or stepwise increases made in the infusion rates, to control increases in systolic arterial pressure or heart rate; if these increases were not controlled by infusions of 0.06 and 0.4 µg kg^{-1} min^{-1} respectively, isoflurane was added.

Remifentanil had the greater effect on the haemodynamic response to intubation, and more isoflurane was used in the patients receiving fentanyl. Recovery at the end of anaesthesia was similar in the two groups, as were the incidences of nausea and vomiting. Again, there was no evidence from preliminary studies of the equipotency of these two regimens.

When used for cardiac anaesthesia, the short context-sensitive time of remifentanil was considered a potential advantage in the "fast tracking" of patients undergoing coronary artery bypass grafting (CABG). In a retrospective comparison with their routine fentanyl–inhalational technique, Bacon and colleagues found no differences between treatments in the haemodynamic responses to surgery.[7] Remifentanil has been shown to attenuate the increases in catecholamines during CABG.[54] While Bacon and colleagues found that their patients receiving remifentanil could be extubated soon after surgery (70% within 3–5 h), this has not been the experience of Duthie and colleagues.[35]

High doses of opioid agonists (alone or in combination with hypnotics or volatile agents) will obtund or abolish intraoperative neuroendocrine responses to pelvic and lower abdominal surgery, but not to upper abdominal, thoracic and cardiac surgery. The three main anilino-piperidine opioids (fentanyl, alfentanil and sufentanil) have all been associated with the occurrence of postoperative respiratory depression.[1 11 66] Several reasons for this have been suggested, including enterogastric recirculation of drug leading to secondary concentration peaks; alterations in body pH and hence increases in the percentage of free opioid in the plasma; and the presence of abnormal drug metabolizers that cause significant reduction of drug clearance.[9 10 114] In the case of alfentanil, the relevance of genetic variability in drug handling has recently become significant (see later).

One of the main reasons for the development of "opioid-alone anaesthesia" was the cardiovascular stability and avoidance of potentially significant drug–drug interactions (for example, the profound hypotension that follows the supra-additive interaction between opioids and benzodiazepines).[117] It has therefore been important to define the therapeutic windows (that is, effective drug concentrations) for opioids and other anaesthetic drugs when used alone or in combination; to quantify factors that affect these windows; and, by the use of computer technology, to provide stable drug concentrations with the aim of achieving defined dynamic effects. However, the concept of closed-loop control of opioid administration is still deficient with respect to the ability to titrate dose (and concentration) in response to changes in patient drug sensitivity.

A major concern when using opioid anaesthesia has been the high incidence of intraoperative awareness. This may be reduced by premedication, or the addition of supplementary agents (nitrous oxide, benzodiazepines, volatile agents or infusions of hypnotics). Although these agents decrease peroperative hypertension and reduce total opioid dosage, with improved recovery and a lower incidence of postoperative respiratory depression, general cardiovascular stability is also reduced.

Pharmacodynamics of opiates used during balanced anaesthesia

MORPHINE AND PETHIDINE

Because blood–brain equilibration is prolonged for morphine and pethidine, there are few data on the interaction of plasma drug concentration and clinical response. However, several authors have studied the concentration–effect relationship for postoperative analgesia. Graves and colleagues defined a minimum effective concentration (MEC) during patient-controlled analgesia (PCA) of 20–40 ng ml^{-1},[47] which was broadly in agreement with the data of Dahlstrom and colleagues, and Gourlay and colleagues.[29 45] However it is only recently that the contribution of the 6-glucuronide of morphine to "total analgesic effect" has been fully realized, and hence estimates of plasma morphine concentrations as indices of analgesia are probably an over-simplification.

We examined "time to first analgesia" after single i.v. doses of morphine 10 mg to supplement volatile–nitrous oxide anaesthesia for general surgery in healthy, benzodiazepine-premedicated patients, and our data support this value for MEC, with plasma morphine concentrations of 50–150 nmol l^{-1}.[112]

In the case of pethidine administered as part of balanced anaesthesia there are few data, and the active metabolite norpethidine is a complicating factor. Austin and colleagues found a relationship between analgesia and pethidine concentrations of the order of 0.5–0.7 μg ml^{-1} for patients undergoing general surgery with balanced anaesthesia.[6] These tally with the findings of Tamsen and colleagues, who showed that mean postoperative plasma pethidine concentration during PCA was 551 ng ml^{-1} and ranged between 130 and 900 ng ml^{-1}.[124] There is the added complication for pethidine of a very steep concentration–effect relationship, such that concentration differences of as little as 0.05 μg ml^{-1} may represent the difference between no analgesia and complete pain suppression.

After i.v. dosing about 65% of pethidine is taken up by the lungs, although it is released back into the circulation within 1–2 min.[103] Plasma protein binding of pethidine is higher than that of morphine (with 70% bound to plasma proteins, mainly α_1-acid glycoprotein, and only a small percentage to albumen). Pethidine is mostly broken down by N-demethylation and hydrolysis to norpethidine, pethidinic acid and norpethidinic acid. The former has some opioid effect, and undergoes renal excretion — so that its effect is more pronounced in patients with renal impairment. Norpethidine also has twice the liability of the parent drug to cause seizures when accumulated in renal failure; this effect is not reversed by naloxone.[81]

ANILINO-PIPERIDINES

The disposition kinetics of fentanyl, alfentanil and sufentanil have been reviewed elsewhere.[16 17 21 41 50 55 56 109] However, several important generalizations on their kinetics are relevant to clinical practice. Sufentanil and fentanyl show no evidence of dose-dependent kinetics,[41] although there is a suggestion that such kinetics may occur with alfentanil.[102] All of the drugs are weak bases, and their ionization is therefore affected by the Henderson–Hasselbach equation.

Fentanyl

Fentanyl shows significant binding to plasma proteins (about 84%), and a high first-pass uptake by the lungs (about 75%), from which it is released in a bimodal fashion.[103,125] Fentanyl binds to both albumen (about 50%) and to α- and β-globulins. Any change in drug binding caused by disease or other interaction may lead to significant alterations in drug dynamics, particularly with respect to respiratory activity.

If we assume that the EEG responds to the concentrations of fentanyl in the brain, these have been shown by Scott and colleagues to parallel those seen in the plasma but with a lag time of about 5 min.[107] The marked hysteresis is accounted for by the drug's lipophilicity and uptake into non-receptor fatty tissues of the central nervous system before binding to its main sites of action. Because of this marked delay in effect, fentanyl should ideally be given about 5 min before the application of a noxious stimulus, or else given in a dose larger than needed so that it saturates the brain and other storage-binding sites. The large volume of distribution of fentanyl also results in considerable variation of plasma concentrations for a given dose,[100] as well as the occurrence of secondary peaks in the concentration–time profile of the opioid at times of altered peripheral blood flow (that is, during recovery from anaesthesia and surgery).

Alfentanil

Alfentanil is less lipid-soluble than fentanyl (heptane: water partition coefficients 2.5 *vs* 9.0), and shows little non-receptor binding in brain tissue. Plasma protein binding of alfentanil is mainly to α_1-AGP and is high (about 90%). At physiological pH, most of the drug is in an un-ionized form because of its low pKa (6.5). Alfentanil has a hepatic extraction ratio of 0.3–0.5, and is mainly metabolized by the cytochrome P450 isoform IIIA3/4, the most abundantly expressed of the hepatic P450 isoforms (20–60%).[62] The role of the isoforms has been further evaluated *in vivo* by the same authors, who then modelled the data to see the influence of isoform induction on the context-sensitive half time of the opioid (fig. 2).[61] The simulations clearly explain part of the variability in the kinetics (and dynamics) of this opioid previously defined as "predictable and short-acting".

Alfentanil has a faster equilibration of the drug concentration between blood and brain (biophase) than is seen with the other fentanyl congeners ($t_{1/2}k_{e0}$: 0.9 min compared with 4.7 and 5.8 min for fentanyl and sufentanil)[106,107] with the exception of remifentanil. Alfentanil dosing is therefore more easily titratable to effect. Studies by Ausems and colleagues[4,5] and Lemmens and colleagues[68,69] have modelled the concentration–dynamic effect relationship when alfentanil by infusion has been given to supplement nitrous oxide. For patients undergoing general surgical procedures, the Cp_{50} plasma concentrations of alfentanil to supplement nitrous oxide–oxygen anaesthesia are shown in table 1. Plasma alfentanil concentrations of about 2000 ng ml^{-1} provide adequate anaesthesia for sternotomy during cardiac surgery.[58]

Sufentanil

Because of the high potency of sufentanil, and poor sensitivity of the radioimmunosorbent assay for measurement of plasma and tissue drug concentrations,

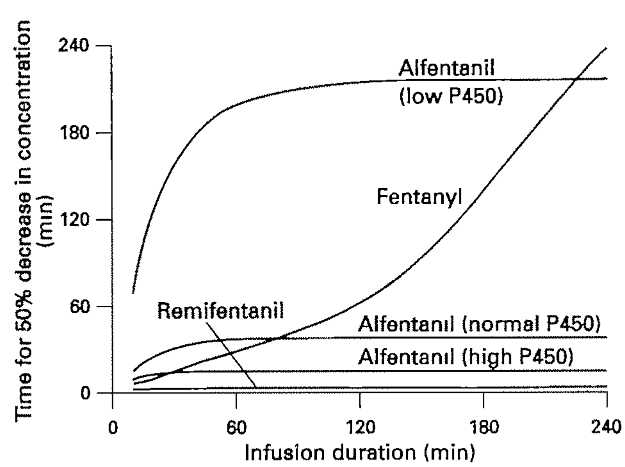

Figure 2 Effect of P450 3A4 activity on the time required for a 50% decrease in alfentanil venous plasma concentration after targetted infusions of various durations The context-sensitive half-times were determined according to the method of Hughes and colleagues.[59] For low P450 3A4 activity an average k_{10} was used (0.080 ± 0.033). Half-times for fentanyl and remifentanil in normal subjects are based on those reported in published studies. Adapted with permission from Kharasch and colleagues.[61]

early kinetic studies of sufentanil were conducted in patients receiving large doses of the drug for cardiothoracic anaesthesia.[14] There are few reliable data sets describing sufentanil's use in balanced anaesthesia,[109] where the kinetics are clearly influenced by the duration of sampling. Gepts and Shafer have examined the drug's disposition after i.v. doses of 250–1500 μg given over 10–20 min, with arterial blood sampling for drug concentrations to 48 h.[41] They defined the kinetics of sufentanil as follows: clearance = 0.92 l min^{-1}; apparent volumes of distribution, V1 = 14.3 l, V2 = 261.6 l, Vss = 339 l; elimination half-life = 769 min. The calculated hepatic extraction ratio for sufentanil was 0.8. Plasma protein binding of sufentanil is in the range 90–92%.[51,52]

In-vitro data suggest that sufentanil binds more tightly than fentanyl to μ receptors, and there is only limited non-specific brain binding. Sufentanil has a pKa of 8.0, and therefore only a small fraction (1.6%) is in the un-ionized form at physiological pH (in comparison with the low ionized fraction of alfentanil at the same pH).

There are fewer data on the dose–effect and concentration–effect for sufentanil as a supplement to nitrous oxide or volatile agents. Our study compared doses of 0.4 and 1.0 μg kg^{-1} sufentanil to supplement nitrous oxide in patients undergoing abdominal or major body-surface surgery.[86] Both doses conferred intraoperative cardiovascular stability, with a duration of effect of about 50 min. Although there is an equilibration delay between blood and biophase for sufentanil, one estimate for intraoperative Cp_{50} is 0.29 ng ml^{-1}[111]; in renal failure, the Cp_{50} was reduced to 0.13 ng ml^{-1} (Sear and Gavaghan, unpublished data).

Remifentanil

Remifentanil is a new opioid that undergoes widespread extrahepatic and hepatic breakdown by tissue and blood non-specific esterases, and therefore has a rapid clearance and short duration of effect.[36,43] The major metabolite of remifentanil is also a pure

Table 1 Concentrations of alfentanil used to supplement nitrous oxide–oxygen anaesthesia in patients undergoing general surgical procedures. (Data from references 4, 5, 68 and 69)

Stimulus	Cp_{50} concentration (ng ml^{-1})
Intubation	475 (28)
Skin incision	279 (20)
Skin closure	150 (23)
Breast surgery	270 (63)
Lower abdominal surgery	309 (44)
Upper abdominal surgery	412 (135)

μ-opioid agonist, but has a potency of only about 1/4600 of the parent compound. This metabolite (GR90291) has been shown by Hoke and colleagues to have a half-life of 19 min in dogs (compared with 5.6 min for remifentanil and 20 min for alfentanil).[52] Using the index of 50% maximum delta EEG activity response, and the 95% spectral edge, remifentanil was 4213–4637 times as potent as the metabolite, although the blood–brain equilibration of the metabolite was significantly faster (0.4 min *vs* 2.3 and 5.2 min respectively).

Remifentanil and fentanyl differ mainly in their kinetics, such that remifentanil can be switched 'on-and-off' very rapidly. This facilitates titration of dose to effect, allowing ready control of responses to noxious and painful stimuli. In excess, remifentanil is associated with the rapid onset of hypotension, bradycardia, apnoea and muscle rigidity; the drug is therefore best given as a short infusion (over 1 min) rather than as a bolus dose, and patients should be pre-treated with anticholinergics if remifentanil is to be used.

Because of its rapid elimination half-life (3–10 min) and context-sensitive half time of 5–10 min even after prolonged infusion, the anaesthetist can give remifentanil at the maximally beneficial rate (for example the ED_{90} rate) without the problems of a prolonged recovery when drug administration ceases.

In assessing the potency of these opioids, several surrogate endpoints have been adopted, such as the drug concentration needed to bring about a half-maximal slowing of the EEG,[37 106 107] or the concentration needed to reduce the MAC of a voltaile agent.[18 44 67 77 131] In the case of remifentanil, the drug is a little less potent than fentanyl, and has an onset similar to that of alfentanil. For the two endpoints described, the potencies can be summarized as follows:

> For EEG slowing, sufentanil is 12 times as potent as fentanyl, while fentanyl and remifentanil are 75 and 16 times as potent as alfentanil.
>
> When assessed on the basis of MAC reduction, the relative potencies of sufentanil, fentanyl, remifentanil and alfentanil are 1:10:10:80.

Rationales for the use of i.v. analgesic drugs

BALANCED ANAESTHESIA

Induction of anaesthesia

Opioid drugs are commonly used as part of an induction sequence to provide a smooth onset to anaesthesia and, more importantly, to obtund the haemodynamic responses to laryngoscopy and intubation.

To achieve onset of anaesthesia with alfentanil alone, McDonnell and colleagues found the ED_{50} dose for loss of verbal command to be 111 μg kg^{-1}.[67] Other opioids (sufentanil, fentanyl and remifentanil) do not appear to offer these same properties of loss of consciousness without the significant side effects of excessive involuntary movements and truncal rigidity.

More recent interest has focused on the combination of opioids with hypnotic drugs or benzodiazepines to provide induction of anaesthesia[80 116 119 126]; the residual analgesia persisting after the induction sequence often prevents the need for further analgesic supplementation, especially when sufentanil or fentanyl have been used. Vinik and colleagues have examined the hypnotic effects of propofol, midazolam and alfentanil in dual and triple combinations. Alfentanil acted synergistically with both midazolam and propofol, but the triple combination showed no greater efficacy than midazolam–alfentanil alone.[127]

MAINTENANCE OF ANAESTHESIA

Administration of opioids to provide intraoperative and often postoperative analgesia may also obtund the haemodynamic responses to intraoperative noxious stimuli. The co-administration of opioids with volatile agents during balanced anaesthesia will also cause significant reductions in the MAC of the volatile agents[44 67 77 131] and intraoperative volatile requirements. However at very high opioid concentrations, there is a "ceiling effect" with no further reduction in the end-tidal volatile concentration (fig. 3). In the case of fentanyl, the steepest reduction in the isoflurane requirement occurs within the analgesic concentration range (0.5–2 ng ml^{-1}).[77]

Because of the longer durations of action of boluses of fentanyl and sufentanil, dosing to supplement nitrous oxide anaesthesia can be satisfactorily achieved with a loading dose followed by bolus increments.[44 86] For alfentanil and remifentanil, continuous infusion is the optimum strategy.[32 45] The rapid response of the patient to changes in plasma concentration of alfentanil or remifentanil (because of their short blood–brain equilibration half-times) allows easy titration of drug dose to clinical response.

Vuyk and colleagues have similarly evaluated an opioid–hypnotic interaction in patients undergoing lower abdominal surgery and receiving an infusion of alfentanil.[129] If the alfentanil infusion is maintained into the postoperative period, computer modelling has defined the optimum combination of propofol–alfentanil to achieve analgesia and the most rapid possible recovery in 50% of patients.[130]

TOTAL INTRAVENOUS ANAESTHESIA

Maintenance of anaesthesia

During total intravenous anaesthesia (TIVA), the required opioid doses and their associated plasma concentrations may vary from those needed during balanced anaesthesia, although TIVA techniques are often used for cardiac and other prolonged surgical procedures where postoperative ventilation is to be carried on.

When an opioid and an hypnotic agent are used to

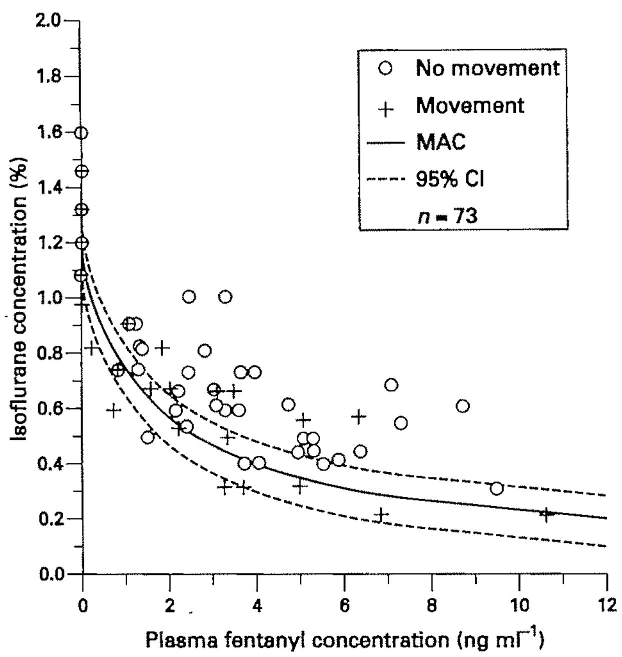

Figure 3 The interaction between fentanyl and isoflurane. The solid line (MAC) represents the concentration of the two drugs that will prevent movement at skin incision in 50% of patients. Adapted with permission from McEwen and colleagues.[77]

provide total intravenous anaesthesia, the drugs interact to potentiate one another. Opioids have been shown by Vinik and colleagues[63 126] to potentiate the hypnotic effects of the benzodiazepines; and in a separate study the interaction of propofol, alfentanil and midazolam were compared in 130 patients who had received no premedication.[77]

However, most of these studies were conducted using single i.v. doses of the various drugs. What happens when infusions of different drugs are administered simultaneously? When midazolam or propofol was used to provide total intravenous anaesthesia, Vuyk and colleagues found that, when alfentanil was given by variable-rate infusion to patients receiving fixed doses of midazolam or propofol, total dose requirements of alfentanil were similar.[128] However recovery to various indices was faster after propofol–alfentanil.

In subsequent evaluations of the propofol–opioid technique, the groups from Leiden and Duke Universities have compared the dose requirements of the two groups of drugs when used to provide anaesthesia. The Cp_{50} for i.v. propofol alone was 3.5 μg ml^{-1} for loss of response to verbal command and about 16 μg ml^{-1} for abolition of response to skin incision.[119] The latter dose can be significantly reduced by the addition of fentanyl or alfentanil.[119 130] Smith and colleagues have shown that increasing the concentration of fentanyl (when given using a target-control system) will reduce the induction concentrations of propofol by 30–40%.[119] During anaesthesia, increasing the opioid concentration reduces the propofol requirement by up to 90%. These interactions are not linear; in the case of propofol–fentanyl, a ceiling effect occurred at fentanyl concentrations of about 3 ng ml^{-1}. There is a similar interaction between alfentanil and propofol.[129 130]

In 1991 Shafer and Varvel described, using computer simulations, the decay profiles of plasma and effect-site concentrations of three commonly used opioids (fentanyl, alfentanil and sufentanil).[115] From these, they showed the anaesthetist how to make an appropriate and rational choice of the correct opioid for surgery of different durations and associated with differing types of noxious stimuli.

For example, because of alfentanil's rapid blood–brain equilibration time and short elimination half-life, bolus dosing is clearly the best when the aim is to obtund acute noxious stimuli. But what if the stimulus lasts longer? For brief-duration infusions (< 30 min), there is little to choose between alfentanil, fentanyl and sufentanil in terms of the speed of offset (although the onset of effect of the latter two is slower than that of alfentanil). For long infusions (> 120 min), alfentanil or sufentanil produce a faster recovery profile than fentanyl. For surgery lasting longer than 240 min, infusions of alfentanil are the preferred option if recovery depends on an 80% decrease in the maintenance opioid concentration, although there is little difference between alfentanil and sufentanil if only a 50% decline is required.

A further elaboration of the concept can be found in the data of Youngs and Shafer,[134] who model the effects of varying infusion durations on not only the 50% decline in plasma drug concentration but also on the 20% and 80% declines (what are termed the "20%, 50% and 80% decrement times"). As the effect site (biophase) concentration is always related to the plasma concentration, the latter is a good descriptor of drug effect except after bolus doses or very short infusions.

Influence of disease on the handling of opioids in man

EFFECTS OF LIVER DISEASE

Because the liver is the main site of opioid metabolism, alterations in drug clearance may be expected in patients with hepatic dysfunction. However, several separate factors interplay one with another, including liver blood flow, liver microsomal enzyme activity, and the binding of drugs to protein and tissue.[57] The increased free fraction observed in liver dysfunction may therefore counter-balance the decrease in mixed-function oxygenase activity.

In patients with cirrhosis, handling of drugs is usually affected because the marked fibrosis and nodular regeneration of the liver cause circulatory changes, such as portosystemic intra- and extra-hepatic shunting; increased plasma volume; increased cardiac output; peripheral pooling of blood; and hypoalbuminaemia. Acute viral hepatitis and alcoholic liver disease predominantly affect the pericentral regions of the hepatic lobules, and are therefore more likely to be associated with impairment of oxidative metabolism. Chronic active hepatitis (CAH) and primary biliary cirrhosis (PBC) affect mainly the periportal regions, and have little effect on drug metabolism. In a study of the handling of alfentanil during anaesthesia in patients with a variety of alcoholic and non-alcoholic liver diseases, we showed differences in drug clearance between control patients, and patients with alcohol-related and non alcohol-related liver disease.[17]

Morphine

Because of the protected locale of those enzymes responsible for glucuronide conjugation, the kinetics of morphine remain unaltered until liver disease reaches the end stage. Approximately 10% of morphine conjugation occurs extra-hepatically in the gastrointestinal tissues and kidney, and in liver disease this can increase to 30%. In severe liver disease, morphine clearance is reduced by 50%, with a doubling of the elimination half-life.[28,79,90] Similarly the bioavailability of orally administered opioids increases.[83,95,96]

In patients undergoing liver transplantation, Bodenham and colleagues showed that if a single bolus of morphine 10 mg was given i.v. at the start of the anheptic phase of the surgery, there was still a rapid decline in plasma morphine levels, suggesting that metabolism might occur during this period.[13] However, during the same period, plasma morphine 3-glucuronide and 6-glucuronide concentrations remained low, although there was a detectable urinary concentration of both metabolites. No normorphine was detectable. It seems likely that the reduced concentration of the parent drug may represent redistribution, as well as possible dilution by infused fluids. Another mechanism might be the uptake of morphine by the lung and other tissues.

Roerig and colleagues, Persson and colleagues, and Ratcliffe all report similar data.[93,99,103] The first two groups observed probably non-significant uptake and no metabolism of morphine (of the order of 0–7%). After a single i.v. dose of morphine coupled with ICG, and collecting the arterial outflow until the peak in ICG was observed, thus avoiding possible contamination through recirculation, Ratcliffe detected no morphine metabolites; but the short sampling period may not have allowed for uptake, metabolism and subsequent release into the pulmonary venous circulation.[99] Overall it seems unlikely that the lung is involved to any great extent in morphine disposition.

Pethidine

In patients with cirrhotic liver disease, the disposition of pethidine shows reduced drug clearance and increased elimination half life,[64,96] but there are no published data looking at the effects of these kinetic changes on the dynamics of pethidine.

In contrast to morphine, there is evidence of significant pulmonary clearance of pethidine. Kramer and colleagues measured lung clearance to account for 46% total clearance in the dog,[65] and this has been supported by values of more than 90% for peak extraction and 65% retention after a single dose before surgery.[103] During a two-stage infusion regimen for postoperative pain relief, there was also significant pulmonary uptake, expressed as the venous-to-arterial concentration difference,[91] but no evidence of overall clearance (as measured by metabolite formation). In the absence of liver function, it seems the lung cannot undertake the hepatic role of biotransformation of these two opioids.

Fentanyl and its congeners

The effects of liver disease on the handling of the anilino-piperidine opioids is complex. In patients with compensated hepatic cirrhosis undergoing surgery, Haberer and colleagues found no change in fentanyl kinetics.[50] However, in patients with severe liver dysfunction undergoing abdominal aortic aneurysmectomy, the elimination half-life of both fentanyl and sufentanil was prolonged.[55,56]

In our comparative study in patients with alcoholic and non-alcoholic liver disease, plasma clearance was lower in non-alcoholic patients than in either alcoholic patients or healthy controls.[17] In all three groups, there was considerable intersubject variability; distribution was bimodal in the non-alcoholic group, in whom there was also a smaller apparent volume of distribution at steady state. The mean residence time was, however, prolonged in the alcoholic group, where plasma protein binding was also decreased compared with controls (84.9% *vs* 89.3%). This was probably attributable to a lower plasma α_1-acid glycoprotein concentration.

There are few data on the dynamic consequences of liver disease on opioid requirements during anaesthesia. However, in patients undergoing breast surgery, Lemmens and colleagues have shown that the Cp_{50} concentration for alfentanil was greater in those with an increased alcohol intake compared with controls.[69] There was also a positive correlation between drug requirements and alcohol consumption.

Remifentanil

Data on the influence of liver disease on remifentanil kinetics are limited, but in patients awaiting liver transplantation, Dershwitz and colleagues showed the disposition of the opioid to be unaltered.[32] However, in the hepatic dysfunction group the remifentanil concentration needed to depress carbon-dioxide-stimulated ventilation by 50% was significantly reduced (1.56 *vs* 2.52 ng ml^{-1}).

EFFECT OF RENAL DISEASE

In the healthy patient, most opioid drugs are metabolized to inactive compounds, which are then excreted in the urine or bile. For example, the hepatic biotransformation of pethidine, alfentanil, fentanyl, sufentanil and morphine may be as high as 80–95%. Phenoperidine differs from these other opioids in that about 50% is normally eliminated in the urine in an unchanged form.

In renal disease, the efficacy of the different opioids may change. The action of phenoperidine, for example, is most likely to be prolonged. Data on opioid efficacy in renal disease are required to prevent opioid dosing that results in significant side effects such as profound analgesia and respiratory depression, so the influence of renal dysfunction on opioid kinetics and dynamics has been evaluated.

Fentanyl, alfentanil, sufentanil and remifentanil

In awake subjects with end-stage renal disease, the kinetics of fentanyl show an increased apparent volume of distribution, and an increased systemic clearance.[24] However, Bower found no change in the plasma protein binding of fentanyl in patients,[15] such that the findings of Corall and colleagues[24] require further confirmation.

Most data from anaesthetized patients with uraemia indicate unaltered fentanyl disposition.[34 48 108] Fentanyl undergoes N-dealkylation and hydroxylation, the metabolites appearing in blood within about 1.5 min of dosing. Binding of metabolites is similar to that of the parent drug, and little free fentanyl appears to be excreted unchanged. The possibility of analgesic activity of the nor-metabolite is uncertain.

Studies evaluating alfentanil disposition indicate an increased free drug fraction in anaesthetized uraemic patients,[16 21] resulting in greater total drug clearance rates and volumes of distribution but no difference in free drug kinetics.

Although sufentanil is not available for i.v. use in the UK, its disposition is similarly unaltered in end-stage renal disease.[30 40 111] There are, however, case reports of prolonged narcosis following administration of sufentanil to patients with chronic renal failure,[40 132] in whom this was probably the result of the opioid's altered dynamics in the uraemic patient.

Recent studies with remifentanil have shown its kinetics to be substantially unaltered in patients with renal disease; there was no change in clearance or volume of distribution, although the elimination half-life was prolonged. Drug dynamics also appeared to be unaffected, with no increased respiratory sensitivity to the drug.[53]

Morphine

In 1975, Olsen and his colleagues showed that the plasma protein binding of morphine in patients with uraemia was decreased, but the free fraction increased only from 65% to 70–75%.[87] There are several reports of prolonged or exaggerated clinical effects when i.v. morphine was given to patients with end-stage renal disease.[33 82 121]

Several authors have confirmed that renal failure *per se* has little effect on morphine parent-drug clearance, but does result in the accumulation of the analgesically active metabolite, morphine-6-glucuronide (M6G).[2 22 104 113 133] The higher concentrations of M6G may account for the profound analgesia and sedation seen in uraemic patients who receive large doses of morphine or papaveretum.[89]

However, in uraemic patients undergoing transplantation who had received i.v. morphine 10 mg as a supplement to anaesthesia with nitrous oxide (67%) in oxygen, the AUC (area under the concentration–time curve between 0 and 24 h) for morphine was larger than that in healthy anaesthetized patients[110] (fig. 4). With the data of Mazoit and colleagues, Sloan and colleagues, and Osborne and colleagues,[79 88 118] our data lend support to the view that the kidney may have a role in morphine metabolism. Whereas the papers of Mazoit and Sloan suggest that around 30–35% morphine elimination may be by non-urinary excretion, non-hepatic degradation — that is, potentially by renal parenchymal metabolism — the two studies in patients with renal failure offer another explanation. The increased plasma morphine concentrations (and larger AUC) could have occurred by hydrolysis of one or other of the accumulating glucuronides (probably the 3-glucuronide) back to the parent compound.

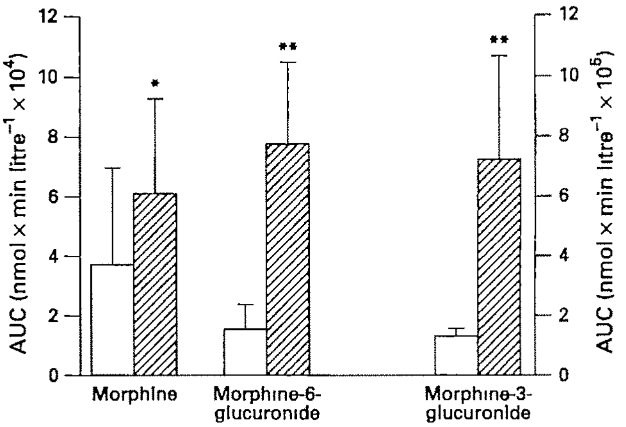

Figure 4 Areas under the concentration *vs* time curve (AUC) for morphine, morphine-3-glucuronide and morphine-6-glucuronide in anaesthetized patients with normal renal function ($n = 5$, open columns) and patients undergoing renal transplantation ($n = 11$; hatched columns) ($*P < 0.05$; $**P < 0.01$) Adapted from Sear and colleagues.[113]

The kinetics of the morphine glucuronides have recently been reported by Loetsch and colleagues, who found half-lives for M3G and M6G in healthy volunteers of the order of 2.8–3.2 h and 1.7–2.7 h respectively.[73] The longer half-lives of M3G and M6G (41–141 h, and 89–136 h) reported by Osborne and colleagues,[89] and Sawe and Odar-Cederlof[104] in patients with impaired renal function may be clinically important in the prolonged effect of the parent drug. Furthermore Sawe has shown a significant correlation between the M3G half-life and the plasma urea concentration; while our own data show a significant correlation between the half-lives of both M3G and M6G and the immediate post-operative 24-h creatinine clearance in the patients undergoing transplantation ($r = 0.87$ and $r = 0.63$ respectively; $P < 0.01$ and $P < 0.05$). However there are insufficient data to derive a nomogram relating plasma creatinine, predicted or measured creatinine clearance, and accumulation of the active M6G in the patient with renal impairment.

The importance of the 6-glucuronide can also be seen in the case reported by Covington and colleagues,[27] where severe respiratory depression was observed in a patient with end-stage renal disease receiving morphine PCA for pain relief after cholecystectomy. The blood morphine concentration was 73 ng ml^{-1} (within the therapeutic range), but the 6-glucuronide level was significantly elevated at 415 ng ml^{-1}.

What then is the contribution of M6G to the analgesic and depressant effects of morphine? In 14 patients with chronic pain (but normal renal function), Portenoy and colleagues assessed the contribution of the glucuronide to overall analgesia when produced by a morphine infusion.[97] Pain relief was greatest when the measured M6G/morphine molar ratio was > 0.7:1, with a significant correlation between the molar ratio and pain relief. In a recent study where volunteers received a tailored infusion of morphine, pain scores were compared with plasma concentrations of both morphine and M6G.[23] The time course of the latter correlated best with the pain score against cutaneous electrical stimulation of the finger, so supporting the hypothesis that M6G contributes significantly to the pharmacodynamics of morphine.

In a further study M6G was given intrathecally to provide an analgesic supplement in patients undergoing total hip replacement under spinal bupivacaine anaesthesia.[46] Postoperative analgesia was supplied by a pethidine PCA system. Although there was no difference between treatments (morphine sulphate 500 μg, and M6G 100 and 125 μg) with regard to time to first analgesia demand, total number of demands, or patients having no postoperative demands, there was an improved visual analogue score for analgesia at rest and on movement in the M6G groups. The incidences of nausea and vomiting were similar in all three groups, but respiratory depression requiring treatment was observed in five patients receiving the glucuronide. Hence the efficacy of M6G is clear, but its safety is questionable.

There are also data to suggest that increased concentrations of another morphine metabolite (normorphine) may be responsible for myoclonic activity, but this has not been confirmed by other researchers.[42] Whether the altered kinetics of morphine and its surrogates are the sole explanation of their prolonged dynamic effect is uncertain. Uraemia is itself associated with CNS depression, and the increased sensitivity to CNS depressant drugs may also be attributable to increased receptor responsiveness, or increased meningeal or cerebral permeability or both.

Pethidine

There are fewer kinetic or dynamic data on the disposition of pethidine in patients with renal failure; the drug is mainly metabolized in the liver, with only 1–5% excreted unchanged in the urine. However Chan and colleagues have confirmed the importance of renal function for the excretion of the metabolite norpethidine.[20] In patients with chronic renal failure, repeated doses of pethidine lead to accumulation of the N-demethylated metabolite, norpethidine. This compound has less analgesic but greater convulsant activity than the parent drug, and Szeto and colleagues described two patients in renal failure where increased plasma ratios of norpethidine/pethidine were associated with excitatory signs.[122]

New drugs

Despite the advances made through the developments of fentanyl, alfentanil, sufentanil and remifentanil, further powerful and potent opioids have been evaluated over the past 5 years, including A3665 (trefentanil); a phenylpiperidine derivative, mirfentanil (a piperidine opioid with both agonist and antagonist properties); and tradamol.

A3665 (TREFENTANIL)

This piperidine opioid acts preferentially at the μ receptor. In a comparison of A3665 with alfentanil in volunteers, Cambareri and colleagues evaluated its analgesic efficacy and ventilatory depression.[19] The two drugs appeared to be approximately equipotent. At doses up to 32 μg kg^{-1}, the test drug causes significant analgesia with a peak effect seen about 3 min after dosing. However, the effect of alfentanil appeared longer-lasting than that of the A3665. At doses of 32 μg kg^{-1} and above there was significant respiratory depression, resulting in significant decreases in oxygenation and increases in carbon dioxide tension in the blood. The peripheral tissue oxygenation also declined to below 90%, although cardiovascular stability was noted at all doses.

Lemmens and colleagues have carried out formal kinetic–dynamic modelling, using the EEG as a surrogate end-point for drug effect.[70] Using these data, computer simulations of recovery after infusions of different duration suggest that A3665 may have significant advantages over alfentanil and fentanyl, but probably not over remifentanil; the times for a 50% decrease in the effect–site concentration range between 60 and 80 min for infusions of alfentanil lasting 4–10 h, but only 15–30 min for A3665. The blood–brain equilibration time of A3665 was slightly longer than that of alfentanil (1.2 *vs* 0.6 min), but both equilibrated faster than fentanyl.

MIRFENTANIL (A3508)

In animal studies, A3508 produced dose-dependent changes in analgesia, but a "ceiling" effect on ventilatory depression. An initial volunteer study evaluated doses of mirfentanil between 12.5 and 400 μg kg^{-1} and compared them with fentanyl 0.75–3 μg kg^{-1}.[75] Mirfentanil showed both analgesic and respiratory depressant effects, but no significant changes in any cardiovascular parameter. However when compared with fentanyl in equipotent analgesic doses, mirfentanil showed a flatter dose–response curve with less depression of ventilation (measured as the increase in arterial carbon dioxide tension). In a subsequent study where mirfentanil was used to provide "conscious sedation" after subarachnoid blockade, incremental doses of 75μg kg^{-1} i.v. were given until the patients' speech became slurred (at a total dose of 9.5 mg, and an associated blood concentration of about 190 ng ml^{-1}).[25] This sedation was accompanied by a further reduction in both mean arterial pressure and heart rate, and there was a decrease in the respiratory rate from 15 to 11 breaths per minute. Oxygen saturation decreased statistically but not clinically (97.7% to 96.1%); however the end-tidal carbon dioxide level did not change.

In a separate patient study using the opioid for conscious sedation, mirfentanil caused anterograde amnesia (as assessed using a yes–no recognition task), coupled with evidence of post-drug impairment of psychomotor activity (using the p-deletion and digit-symbol substitution tests).[26]

Dynamic–kinetic evaluation was again carried out using the EEG as the surrogate end-point measure of drug effect, with butorphanol used as a "control" for comparison of mixed agonist-antagonist drug effects.[71] With both drugs there were significant side-effects: nausea and hallucinations and, with mirfentanil, two cases of epileptiform activity on the EEG, with one of the volunteers progressing to a generalized convulsion.

Both mirfentanil and butorphanol caused a significant tachycardia and ventilatory depression. Mirfentanil (when infused at a rate of 25 μg kg^{-1} min^{-1}) had greater cardiovascular effects during and after drug dosing. The kinetics of mirfentanil showed an elimination half-life of around 300 min, clearance of 5.8 l min^{-1}, and apparent volume of distribution at steady state of 247 l.

Because of the marked inter-individual variability in the EEG patterns with both drugs and, in the case of mirfentanil, an absence of slowing of cerebral rhythms, it was not possible to use the EEG as a measure of analgesic action on the brain. Data obtained after this study was completed indicate that mirfentanil is not a mixed agonist–antagonist, but rather a partial μ, partial delta, and negligible kappa opioid agonist. Because of these significant and serious cardiovascular and CNS effects, mirfentanil is not being further evaluated.

Tramadol

Tramadol is another phenylpiperidine derivative, with a structure similar to that of pethidine. The limited kinetic data of the drug show an elimination half-life of 5–7 h, and clearance of 7–10 ml kg^{-1} min^{-1}. It is a drug that binds to sigma and kappa receptors with weak affinity as well as to the μ receptor, where it exerts moderate activity. Tramadol also has actions at the monoamine receptors of the sympathetic nervous system, where it acts to prevent amine re-uptake, as well as possibly displacing stored 5-HT from nerve endings.

Tramadol exists as a chiral mixture, and there are separate identifiable actions of the different stereoisomers, namely the (+) isomer seems to bind to the μ receptor, while the (–) isomer is responsible for monoamine re-uptake inhibition. Through this dual action, the analgesic activity is only partially antagonized by naloxone; there is also partial inhibition of analgesia by two antagonists (such as yohimbine) and serotoninergic blockers.

On comparison with morphine, tramadol has a potency of about 1/5th to 1/10th but causes less respiratory depression.[38] In a randomized, double-blind comparison with extradural morphine when used to provide analgesia after thoracotomy, James and colleagues found no differences between the treatments (tramadol 150 mg and morphine as a 2 mg bolus and an infusion of 0.2 mg h^{-1}) in terms of patients' need for additional opiate pain relief using PCA morphine.[60] There were also no differences in the circulating levels of plasma epinephrine and norepinephrine, nor evidence of respiratory depression.

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Remifentanil and tramadol

D. J. R. DUTHIE

Remifentanil (Ultiva, Glaxo Wellcome) and tramadol (Zydol, Searle; Tramake, Galen; Zamadol, ASTA Medica) represent two contrasting approaches by pharmaceutical companies to improve the clinical treatment of pain. Remifentanil has the same mode of action as existing pure μ opioid analgesic drugs, but because of its rapid esterase metabolism it has an ultrashort duration of action. The drug has therefore to be given by continuous i.v. infusion, but any drug effects can be rapidly controlled. Tramadol and its active metabolite have low affinities for the μ opioid receptor, but inhibit reuptake of norepinephrine and enhance secretion of serotonin, achieving modulation of pain in the central nervous system. Clinicians are offered the chance to take advantage of new phamacokinetics and new pharmacodynamics to treat pain in clinical practice.

Remifentanil

Remifentanil (fig. 1) is the hydrochloride salt of 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phynylamino]-1-piperidine] propanoic acid, methyl ester. It is a short-acting, synthetic, esterase-metabolized opioid, with a side branch susceptible to rapid hydrolysis by non-specific blood and tissue esterases to an acid, GR90291.[29] It is presented as a lyophilized powder for reconstitution with water. The preparation is a white crystalline powder, readily soluble in water with a pKa of 7.07. The aqueous solution has a pH of 4.5. The vials contain hydrochloric acid and glycine USP 15 mg vial^{-1}. Glycine is an inhibitory neurotransmitter, which renders the preparation unsuitable for extradural or subarachnoid injection. Once reconstituted in water then diluted with dextrose 5% down to concentrations of 20 μg ml^{-1}, the solutions remain stable at room temperature for up to 24 h.

MODE OF ACTION

Remifentanil is an effective agonist at the μ opioid receptor and produces profound analgesia. This effect is antagonized effectively by naloxone.[29] The drug differs from existing highly effective opioid agonists in its rapid metabolism by nonspecific red-cell and tissue esterases, rather than in any novel properties at the opioid receptor.

INDICATIONS AND CONTRAINDICATIONS

Remifentanil is indicated for use as a supplement to general anaesthesia during induction and as an analgesic during maintenance of anaesthesia.[48] It is effective in blunting haemodynamic responses to stimuli during anaesthesia. Clinical studies have compared heart rate and systemic arterial blood pressure in groups of patients given remifentanil or alfentanil as the opioid, in part of an anaesthetic technique balanced by muscle relaxant and inhalation or i.v. anaesthetic agent; there are consistently fewer responses to remifentanil in the doses used. Responses to intubation and skin incision measured by rises in heart rate and blood pressure occurred in 15% and 8% of patients given remifentanil 1.0 then 0.5 μg kg^{-1} min^{-1}, and 28% and 17% with alfentanil.[50] During outpatient laparoscopic surgery, 11% of patients given remifentanil 1.0 then 0.5 μg kg^{-1} min^{-1} responded to insertion of the trochar compared with 32% of patients given alfentanil. Responses at any time during surgery were demonstrated by 53% of patients given remifentanil compared with 71% in the alfentanil group.[42]

Obtunding haemodynamic response is dose related until 1.0 μg kg^{-1} min^{-1}. At intubation, heart rate and blood pressure were significantly lower in patients given remifentanil 1.0 μg kg^{-1} min^{-1}, 75.2 (20.4(SD)) min^{-1} and 114.6 (28.2) mm Hg, than in those given remifentanil 0.5 μg kg^{-1} min^{-1}, 68.5 (14.8) min^{-1} and 125.2 (34.3) mm Hg, although the differences were not significant clinically.[23] Before cardiac surgery 93% of patients suffered no haemodynamic response to sternotomy and maximal sternal spread when given remifentanil 1.0 μg kg^{-1} min^{-1} and propofol 50 μg kg^{-1} min^{-1}. There was no improvement on increasing the dose to 1.5 and 2.0 μg kg^{-1} min^{-1}, when responses to sternotomy and maximal sternal spread were 89% and 91% respectively.[49]

There is the customary opioid effect on spectral edge (SE$_{95}$), where the frequency of the EEG spectral edge falls with increasing effect-site concentration in a sigmoid relationship.[38 16] However, remifentanil does not reliably produce loss of consciousness. Over a dose range of 2–20 μg kg^{-1} the ED$_{50}$ of 12 μg kg^{-1} and EC$_{50}$ of 53.8 ng ml^{-1} for loss of consciousness were far in excess of doses used clinically and were associated with severe muscle rigidity. Remifentanil is not recommended as a sole anaesthetic agent and should be given in association with an inhalation or i.v. anaesthetic agent.[30] Similarly, for sedation during surgical procedures under local anaesthesia, better

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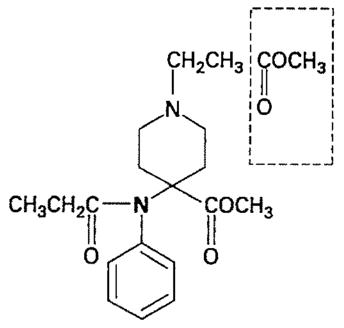

Figure 1 Remifentanil. The box indicates the site of nonspecific esterase metabolism.

results were obtained using remifentanil with midazolam 2 mg i.v. than with remifentanil alone. When infusing remifentanil and titrating infusion rate to effect, introducing midazolam reduced the rate of remifentanil required from 0.12 (0.05) to 0.07 (0.03) μg kg^{-1} min^{-1} and resulted in less nausea.[20] Equally, when infusing remifentanil and titrating it to effect with placebo or midazolam 2, 4, or 6 mg i.v., remifentanil alone was found to be less satisfactory than remifentanil 0.05–0.1 μg kg^{-1} min^{-1} with midazolam 2 mg i.v.[2]

The amount of anaesthetic supplement required to achieve anaesthesia is considerably reduced by remifentanil. Using computer-controlled infusions to achieve target remifentanil concentrations of 0–32 ng ml^{-1}, remifentanil 1.37 ng ml^{-1} achieved a 50% reduction in minimum alveolar concentration (MAC) of isoflurane required to prevent movement on skin incision from 1.3% without remifentanil. Remifentanil 2–4 ng ml^{-1} achieved a 70% reduction in MAC and remifentanil 32 ng ml^{-1} a 91% reduction. Even at very high concentrations, remifentanil without isoflurane did not provide adequate anaesthesia. Blood remifentanil clearances of 28–35 ml min^{-1} kg^{-1} were calculated.[33] At steady state, when infusion rate = concentration at steady state × blood clearance, remifentanil 0.038–0.048 μg kg^{-1} min^{-1} would be required to achieve a 50% reduction in MAC for isoflurane. This is at the lower end of the dose range recommended for clinical anaesthesia. The use of remifentanil as the mainstay of an anaesthetic technique, with doses of anaesthetic agent much lower than those required when using small opioid supplement, forms the basis of anaesthesia based on "esterase metabolized opioid" advocated by Glaxo Wellcome. The effect of excessive inhalation or i.v. agents in the presence of remifentanil at times of minimal surgical stimulation may be responsible for episodes of hypotension, reversed promptly by simple measures, seen during remifentanil infusion.[49]

Remifentanil is an effective opioid supplement but, because of its rapid offset, patients will experience immediate pain after emergence from anaesthesia unless there is an effective strategy to treat pain after operation. Following abdominal surgery under remifentanil/propofol total i.v. anaesthesia, 86% of patients experienced no or mild pain in the recovery room with a continuous infusion of remifentanil reduced to 0.086 μg kg^{-1} min^{-1}. Patients were then changed to postoperative extradural analgesia or patient-controlled morphine i.v. Subsequently, in the surgical ward, patients receiving extradural analgesia achieved better pain scores than did those using patient-controlled analgesia.[5] Remifentanil infusion 0.05–0.23 μg kg^{-1} min^{-1} provided better analgesia after abdominal surgery under total i.v. anaesthesia, when 58% of patients experienced no or mild pain compared with 33% of those receiving intermittent morphine i.v. However, moderate or severe pain was experienced in 74% of patients after removal of the tracheal tube, and the effects of remifentanil dissipated promptly after discontinuation of the infusion.[58] After abdominal surgery initial infusions of remifentanil 0.1 μg kg^{-1} min^{-1} provided better anaesthesia than 0.05 μg kg^{-1} min^{-1}. Once the drug was titrated to effect, 71% of patients reported no or mild pain with an adequate rate of spontaneous ventilation.[50]

ADVERSE EFFECTS OF REMIFENTANIL

The familiar adverse effects of an opioid—respiratory depression, sedation, nausea and vomiting, muscle rigidity, bradycardia and pruritus—are demonstrated.[29 19 17] Like the analgesic effects of remifentanil, the adverse effects are short-lived and antagonized by naloxone.[1] Remifentanil has not been associated with histamine release.[51] In patients breathing spontaneously, the onset of life-threatening muscle rigidity and apnoea can be alarmingly rapid. Injection of 0.5 μg kg^{-1} doses in less than 10 s and large infusion rate increases within 2 min of a previous increase were more likely to be followed by muscle rigidity and apnoea.[50] These effects dissipated rapidly when the drug was withheld and may be avoided by spreading injection of single doses over 30 s and changing remifentanil infusion rates no more frequently than at 10-min intervals. During operation, bradycardia was more likely during abdominal surgery in patients given remifentanil than alfentanil,[50] and in children undergoing strabismus surgery the oculocardiac response was more marked with remifentanil than alfentanil.[10] There was little change in heart rate in patients who received remifentanil during cardiac surgery in the presence of the vagolytic muscle relaxant, pancuronium.[49]

DOSE

Remifentanil is recommended for induction of anaesthesia as an infusion of 0.5–1 μg kg^{-1} min^{-1} with or without 1 μg kg^{-1} injected i.v. over 30 s. During maintenance of anaesthesia an analgesic infusion of 0.05–2 μg kg^{-1} min^{-1} is given, with supplemental doses as required should light anaesthesia be suspected. When patients are breathing spontaneously an initial infusion of 40 ng kg^{-1} min^{-1} is then adjusted, usually to within the range 25–10 ng kg^{-1} min^{-1}. Early clinical experience of remifentanil has been obtained within sponsored drug trials undertaken to gather data for regulatory authority approval. Subsequent experience in routine clinical practice may well limit the 40-fold dose range for analgesic supplement and demonstrate reduced requirements for concurrent inhalation and i.v. anaesthetic agents.

PHARMACOKINETICS

Remifentanil arose from a deliberate attempt to develop a 4-anilido piperidine compound with opioid effects and a very short duration of action.[18] Within the molecule is an ester side branch (fig. 1) that is crucial to its opioid activity and susceptible to hydrolysis. The distinctive pharmacokinetics of remifentanil are a result of the drug being rapidly metabolized by non-specific red blood cell and tissue esterases, like the beta-adrenoceptor antagonist esmolol[57] and calcium antagonist clevidipine.[41] This rapid esterase metabolism distinguishes remifentanil from other opioids and will determine its place in clinical practice.

Extensive metabolism occurs in blood cells and muscle that is unaffected by isolated organ failure. The pharmacokinetics and respiratory effects of remifentanil are unchanged in patients with end-stage hepatic[13] and renal disease.[9, 26] The major metabolite GR90291 is itself a μ opioid agonist and is excreted by the kidney. The metabolite accumulates in renal failure, but its activity is only 1/4600 that of the parent compound; only if there was substantial accumulation could the metabolite exert a clinically important opioid effect.[24] In the liver, in the same way that fentanyl is metabolized, there is a minor pathway of N-demethylation for remifentanil. The lung does not clear remifentanil from the circulation.[14]

The esterase metabolism suffered by remifentanil is not related to pseudo-cholinesterase (butyrlcholinesterase), which terminates the action of suxamethonium. Remifentanil is not a substrate for pseudo-cholinesterase and patients who are deficient in pseudo-cholinesterase and therefore susceptible to suxamethonium apnoea, metabolize remifentanil normally.[54]

Remifentanil is 70% bound to α-1-acid glycoprotein. Its *in vitro* metabolism is significantly reduced by dilution with albumin, which may bind to remifentanil and prevent metabolism by red-cell esterases.[11] The high protein binding contributes to its volume of distribution at a steady state of 0.3–0.4 litre kg^{-1}, which is smaller than that of other opioids. Because of this, and its rapid metabolism and large clearance of 2.9 (0.4) litre min^{-1} or 174 (24) litre h^{-1},[15, 31] the terminal elimination half-life of remifentanil is extremely short, with a mean of 9.52 (3.95) min.[19] Consequently, remifentanil must be delivered by continuous infusion i.v. with or without a loading dose to be useful clinically. It is possible to dilute any opioid for injection i.v. and deliver it by continuous infusion, but remifentanil, of all the available opioids, best satisfies by far the five requirements of a drug necessary to make rate-controlled delivery worthwhile: short elimination half-life; no active metabolites; offset by metabolism or excretion and not redistribution; a concentration–effect relationship; and a narrow therapeutic index.[44]

Another distinction between remifentanil and other opioids is the behaviour of the drug after prolonged infusion. Early safety studies of single doses of a drug in healthy volunteers generated pharmacokinetic data summarized by variables such as elimination half-life, rate constants, clearance and volume of distribution. Far from being immutable, these variables may change markedly with larger doses, repeated doses or continuous delivery, and may vary with the duration of therapy. The consistency of the pharmacokinetics of remifentanil with prolonged infusion contrasts markedly with changes in pharmacokinetic values obtained with other opioids after prolonged administration.

Of the main pharmacokinetic variables, half-life is easiest to comprehend, because time is a familiar unit of measurement. However, half-life alone gives little information about the behaviour of a drug in a single-compartment model and predicts less of the behaviour of a drug better described by two- or three-compartment models.[52] A more useful descriptor, "context-sensitive half-time" has been proposed, where "context" refers to the duration of infusion and the "half-time" is the time required for the drug concentration in the central compartment to decline by half after a particular duration of infusion.[27]

The difference between single injection and prolonged infusion arises when distribution from central to peripheral compartments is responsible for a considerable part of the offset of action of a drug. After prolonged infusion, the peripheral-compartment drug concentration tends to equilibrate with the central-compartment concentration. When the infusion is stopped there is no opportunity for offset of drug action by distribution from central to peripheral compartment and the offset of action is delayed relative to the offset after single injection. By declaring the context of duration of infusion, subsequent central-compartment half-times of different drugs may be calculated and compared.

However much of an improvement context-sensitive half-time may be, it remains a pharmacokinetic variable of use in predicting only drug concentrations, albeit in the central compartment. If these concentrations are to be used to derive a prediction of drug effect, it is necessary to take into account the influence of delay caused by a drug equilibrating between the central compartment and site of action. This may be calculated by considering the site of action as an effect compartment with a rate constant $ke0$ between central and effect compartments. The equilibration half-life, $t_{1/2}ke0$, is calculated from the ratio of $\ln(2)/ke0$. For drugs like remifentanil, whose $ke0$ is large, the difference between pharmacokinetic and pharmacodynamic context-sensitive half-times will be small.

For drugs whose concentration–effect relationship is described by a sigmoid curve, the central portion may demonstrate a linear relationship between drug concentration at the effect site and clinical response. Even then, the ability of the calculated central-compartment concentration to predict drug effect is hindered by the equilibration time between central compartment and effect site. For remifentanil this equilibration time is very short. The $t_{1/2}ke0$ was 1.3 min for effect on minute volume of ventilation. The change in minute volume% followed closely the same time course as blood concentrations.[19] Modelling changes in spectral edge on the EEG, $t_{1/2}ke0$ was 1.34 min.[38] These rate constants are dependent on age. In the elderly, modelling of pharmacokinetic and EEG data suggest that single doses of remifentanil should be halved and infusions run at a third of the rate compared with doses intended for healthy adults.[39]

The pharmacokinetics of remifentanil make blood concentrations predictable. Remifentanil blood concentrations obtained by infusions of 1.0–2.0 μg kg^{-1} min^{-1} were related linearly to the rate of infusion and

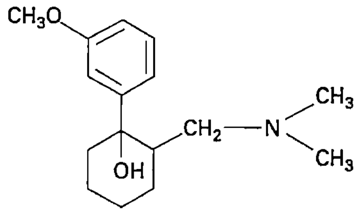

Figure 2 Tramadol.

unrelated to the duration of infusion,[14] unlike those of fentanyl and alfentanil, which demonstrate accumulation.[17 31]

SUMMARY

Remifentanil is a highly effective opioid analgesic with a short half life, predictable pharmacokinetics and a close concentration–effect relationship. It offers the best available opportunity to control opioid effects. However, care must be taken to ensure that infusion rates are set appropriately to control pain and responses to surgical stimuli without inducing life-threatening respiratory depression and muscle rigidity, the onset of which can be rapid.

Tramadol

Tramadol (fig. 2), (+)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol hydrochloride, is presented as a racemic mixture of two enantiomers. It is available as capsules and soluble tablets of 50 mg and as a solution of 50 mg ml^{-1} for i.v. or i.m. injection.

MODE OF ACTION

The analgesic mode of action of tramadol is not fully understood. It has demonstrable analgesic properties, but its effects are distinct from those of the pure μ opioid agonists available in clinical practice. Initially considered an opioid analgesic, it has a weak affinity for μ opioid receptors. In the mouse tail-flick test, the antinociceptive activity of tramadol was completely antagonized by naloxone and both tramadol and morphine have failed to demonstrate antinociceptive activity after intracerebroventricular injection in CXBK mice.[47]

The (+)-M1 metabolite, *O*-desmethyltramadol, has a higher affinity than tramadol for opioid receptors. This demethylation is blocked by quinidine, a potent CYP2D6 inhibitor. The opioid activity of tramadol may well be consequent to metabolism of the parent drug to the active demethylated metabolite by the polymorphic cytochrome P450 enzyme, debrisoquine 4-hydroxylase (CYP2D6).[8 43]

Tramadol was discovered subsequently to inhibit reuptake of norepinephrine and promote release of serotonin. The contribution of enhanced monoaminergic transmission to the analgesic actions of tramadol is supported by the blocking of antinociceptive effects of intrathecal tramadol, but not those of morphine, by yohimbine and ritanserin.[47] The reversal of the antinociceptive effects of tramadol by these α_2-adrenoceptor antagonists suggests that tramadol achieves monoaminergic spinal modulation of pain through indirect activation of postsynaptic α_2-adrenoceptors, blocking impulses reaching the brain. The synergy of monoaminergic and opioid activity achieves analgesic effects.

Tramadol is a racemic mixture. Each enantiomer has different opioid binding affinities and they differ in their inhibition of monoaminergic re-uptake inhibition.[46]

INDICATIONS AND CONTRAINDICATIONS

Tramadol is indicated for moderate to severe pain in adults. It has the same analgesic potency as pethidine, 1/5 of that of nalbuphine, 1/1000 that of fentanyl and 1/10 that of morphine i.v. Tramadol 50–150 mg i.v. was equivalent to morphine 5–15 mg i.v., but a preservative-free preparation had only 1/13 of the potency of morphine extradurally.[40]

Despite being relatively less potent than pure opioids, tramadol has achieved efficacy when used to treat moderate pain after surgery. In treating pain after thoracotomy, tramadol 150 mg i.v. was no different in effect to morphine 2 mg extradurally combined with an extradural infusion of 0.2 mg h^{-1}, but in the first 24 h after surgery patients required mean rescue doses of morphine 27.2 (16.9 (SD)) mg i.v. and 34.2 (15.7) mg i.v. respectively by patient-controlled analgesia.[28] After hysterectomy, tramadol 50 mg i.v. was as effective as morphine 5 mg i.v. in treating pain described as moderate; pain assessment was by serial changes in verbal rating scores after analgesic administration. By the same assessment, tramadol was less effective than morphine in relieving pain described as severe.[26] Because of its efficacy as an analgesic, tramadol is considered to be effective in step two of the World Health Organisation guidelines for the treatment of patients with cancer pain.

As tramadol enhances monoaminergic transmission, the drug is contraindicated in patients receiving monoamine oxidase inhibitors[22] and caution is advised in patients with epilepsy. It is not recommended for children.[55]

ADVERSE EFFECTS OF TRAMADOL

There have been reports of dizziness, nausea, sedation, dry mouth and sweating, but this particular pattern of adverse effects may offer advantages in patients for whom opioids and non-steroidal anti-inflammatory drugs are not suitable.

Respiratory depression with tramadol is less than with morphine, and has features that differ clinically from those of opioid respiratory depression. Patients breathing spontaneously under halothane anaesthesia had a transient fall in respiratory rate without change in end-tidal carbon dioxide concentration after tramadol 0.5–2.0 mg kg^{-1} i.v., but demonstrated apnoea or considerable respiratory depression after morphine sulphate 0.143 mg kg^{-1} i.v. It was concluded that tramadol had no clinically relevant respiratory depression.[56] In patients breathing spontaneously after major abdominal surgery, with analgesia provided by extradural lidocaine in combination with extradural tramadol 100 mg or morphine 4 mg, morphine but not tramadol produced a fall in arterial oxygen tensions when patients breathed air. Neither drug was associated with a rise in arterial carbon dioxide tensions and the incidence of itching, nausea and vomiting was no different between the two.[5] After tramadol 50 mg or morphine 5 mg i.v. in patients after gynaecological surgery, peripheral haemoglobin oxygen saturation did not fall below 86% in patients given tramadol, but did fall below this value in 13.3% of patients given morphine i.v. 86%.[26] After lateral thoracotomy in patients given tramadol 150 mg i.v. or morphine 2 mg and 0.2 mg h^{-1} extradurally, measurements of arterial oxygen tension were higher and those of carbon dioxide tension were lower at 2 and 4 h after surgery in patients who received tramadol.[28] Respiratory depression is unusual in recommended doses and was not found in neonates whose mothers had been given tramadol.[12] The advantage of tramadol over opioids with respect to reduced respiratory depression is limited by the lack of efficacy of tramadol in severe pain, where opioids are more effective.

Unlike non-steroidal anti-inflammatory drugs, tramadol does not inhibit prostaglandin synthesis. Patients with peptic ulceration, renal impairment and asthma may avoid drug-induced exacerbations of these diseases by substituting tramadol for non-steroidal anti-inflammatory drugs. Unlike morphine, tramadol does not elicit histamine release and so does not cause skin flushing and idiosyncratic hypotension.[4]

Although tramadol is substantially haemodynamically stable, transient haemodynamic effects have been recorded after injection i.v.. During anaesthesia, systolic arterial pressures rose 14–16 mm Hg and diastolic pressures rose 10–12 mm Hg for 4–6 min, returning to baseline within 15 min. Postoperatively the blood pressure rise was only 6–9 mm Hg after 1.5 mg kg^{-1} tramadol i.v. Associated with the changes in systemic arterial pressures, peripheral vascular resistance rose 25% at 2–10 min after injection and there was an increase of 15–20% in the work of the heart over the same period.[40] No clinically significant change in heart rate was demonstrated during postoperative infusion i.v.[6]

Reported gastrointestinal effects of tramadol include nausea, vomiting and constipation, but to a lesser extent than with opioids. There was no increase in the baseline pressure or duration, frequency and amplitude of contractions of the bile duct sphincter when tramadol was given i.v. to patients during endoscopic retrograde cholangiopancreatography (ERCP).[53]

Tramadol has not been recommended for use as an analgesic supplement during light planes of general anaesthesia because of increased postoperative recall.[36] The anaesthetic technique used involved fentanyl, droperidol and atropine premedication, methohexitone induction and maintenance by nitrous oxide 79% in oxygen. Enflurane was delivered when indicated clinically and patients received either tramadol or saline by infusion. There was no difference between tramadol and placebo patients in the duration or dose of enflurane used, but 65% of patients receiving tramadol and none receiving placebo could recall the music played to them under anaesthesia. As a supplement to anaesthesia including diazepam premedication, propofol and suxamethonium induction and mechanical end-expired concentrations of nitrous oxide 66% and isoflurane 0.7% in oxygen, tramadol 100 mg and 200 mg i.v. obtained minor electroencephalogram changes, no movement to skin incision and no spontaneous conscious recall.[7] The lightening of anaesthesia and increased postoperative recall found with tramadol during anaesthesia with nitrous oxide in oxygen was not reproduced using a technique that included an inhalation anaesthetic agent throughout maintenance of anaesthesia.

Tramadol has a low potential for abuse i.v. in clinical doses and is a prescription-only medicine rather than a drug controlled by the Misuse of Drugs Act. In contrast to morphine in doses of 15 and 30 mg i.m., which was recognized as an opioid by non-dependent opioid abusers and produced subjective effects and miosis, tramadol in doses 75 and 150 mg i.m. was not recognized as an opioid. Tramadol 300 mg was recognized as an opioid, but produced no other morphine-like effects or miosis.[45] Whereas nalbuphine, buprenorphine and morphine elicit tolerance and cross-tolerance, this was not observed with tramadol in arthritic-induced rats after repeated administration of tramadol twice daily for 4 days.[32]

DOSE

Tramadol is recommended in a dose of 50–100 mg orally every 4 hours. A total of more than 400 mg per day by mouth is not usually required. Postoperatively, an initial dose of 100 mg i.v. then 50 mg every 10–20 min up to a maximum of 250 mg in the first hour and 600 mg in 24 h (BNF) may be given.

PHARMACOKINETICS

Oral tramadol is rapidly absorbed and has a bioavailability of 68% after a single dose and 90–100% after multiple doses. Tramadol begins to appear in plasma after 15–45 min and reaches peak plasma concentrations at 2–4 h. Regular dosing will achieve steady state within 2 days. It has a high tissue affinity with a volume of distribution of 306 and 203 litres after oral and i.v. administration. There is 1% placental transfer. Tramadol is 20% bound to plasma protein with an elimination half life of 5.1 (0.8) h. Liver metabolism accounts for 86% of the absorbed dose by *N*- or *O*-demethylation with subsequent sulphation or glucuronidation. The (+)-M1 metabolite *O*-desmethyltramadol is an agonist at the opioid receptor with a higher affinity than the parent compound and a half life of 9 h. Ninety per cent of an oral dose is excreted via the kidneys, the remainder in faeces.[12 21 34 37]

In patients with chronic renal failure and a creatinine clearance of <30 ml min^{-1}, the dose of tramadol should be reduced to a maximum of 200 mg per day in 12-hly divided doses. With hepatic cirrhosis, the elimination half life is doubled and the maximum dose of tramadol should be further reduced to 50 mg every 12 h. When induction of hepatic enzymes with, for example, carbamazepine 400 mg twice daily occurs, the dose of tramadol can be doubled to compensate for the enhanced hepatic clearance. There has been no correlation demonstrated between plasma tramadol and analgesic effect.[35]

SUMMARY

The lack of analgesic efficacy limits tramadol as a sole agent to treat severe pain after surgery. However, it has a relative lack of respiratory depressant and constipating effects compared with morphine and codeine, and does not share the propensity of non-steroidal anti-inflammatory drugs to provoke asthma, gastrointestinal mucosal damage and renal impairment. It may well have a place in the management of pain after surgery, in combination with another drug, such as paracetamol, or after control of the worst of pain after surgery by a regional local anaesthetic technique.

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Opioid tolerance: the clinical perspective

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Uncertainty about the clinical significance of tolerance to opioid analgesia has important and diverse implications. Although understanding of the characteristics and mechanisms of experimental tolerance has grown, the clinical correlates and ramifications of these findings remain ambiguous to practitioners prescribing long-term opioid therapy to patients for the treatment of malignant and non-malignant pain. In this review I shall discuss clinical aspects of tolerance and the associated phenomena of dependence, withdrawal and addiction to opioids as they apply to the practice of clinicians who manage patients with chronic malignant and non-malignant pain.

Why is tolerance important?

Most cancer pain can be successfully treated using pharmacological measures based on simple principles promoted by the World Health Organisation[100] and extensively validated.[94 103] Opioid medication, commonly oral morphine, is the third step on the 'analgesic ladder' and has been widely used for the management of acute and chronic cancer pain for many years, providing excellent analgesia without respiratory compromise often for months or even years.[38 92]

However, morphine has long been feared by the general public and by doctors. Concerns about addiction and tolerance are common among cancer patients. Hodes questioned 40 patients with metastatic cancer taking opioids and their spouses on a variety of issues related to cancer pain. Forty-five percent of patients and 43% of their spouses reported either moderate or extreme concern about addiction to their medications, and concerns about tolerance were expressed by 50% of patients and 63% of their spouses.[40] Recent interest in euthanasia has resulted in media coverage that portrays morphine as the physician's ultimate weapon to cause respiratory depression and subsequent death in patients who are terminally ill.[3 32] Fears evoked by these concerns may have an impact on compliance with regular analgesia and medication for breakthrough pain.

Current interest in the prescription of opioids for non-malignant pain and in the development of potential guidelines in this area has also made the complex phenomena of tolerance, physical dependence and addiction increasingly important to the clinician.[35 62 71 73 75]

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Keywords: analgesics opioid; pain, chronic; cancer; children; opioid addiction; opioid tolerance

Nomenclature of tolerance and related phenomena

Confusion exists among physicians who treat patients with cancer pain about the definitions of tolerance and related phenomena,[47 97] and understanding of the precise terminology is important.

TOLERANCE

Tolerance refers to a phenomenon in which exposure to a drug results in the diminution of an effect or the need for a higher dose to maintain an effect.[45]

There are various types of tolerance, as shown in table 1.[67]

Innate tolerance refers to the genetically determined sensitivity (or lack of sensitivity) to a drug that is observed the first time that the drug is administered. Acquired tolerance can be divided into three types: pharmacokinetic, pharmacodynamic and learned tolerance.

Pharmacokinetic or dispositional tolerance refers to changes in the distribution or metabolism of the drug after repeated drug administrations that result in reduced concentrations in the blood and subsequently at the sites of drug action. The most common mechanism is an increase in the rate of metabolism of the drug, as in the case of barbiturates.

Pharmacodynamic tolerance refers to adaptive changes that have taken place within systems affected by the drug, such as drug-induced changes in receptor density, so that response to a given concentration of the drug is reduced.

Learned tolerance refers to a reduction in the effects of a drug as a result of compensatory mechanisms that are learned. One type of learned tolerance is behavioural tolerance. This describes the skills that can be developed through repeated attempts to function when in a state of mild to moderate intoxication – a common example is learning to walk a straight line in spite of motor impairment produced by alcohol intoxication. This probably involves both acquisition of motor skills and a learned awareness of

Table 1 Types of opioid tolerance

- Innate
- Acquired
  - Pharmacokinetic
  - Pharmacodynamic
  - Learned tolerance
    - Behavioural
      - Conditioned

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the deficit that causes the individual to walk more carefully.

A special case of behavioural tolerance is referred to as conditioned tolerance. Conditioned tolerance (situation-specific tolerance) is a learning mechanism that develops when environmental cues are consistently paired with the administration of the drug. When a drug affects homoeostatic balance by producing sedation and changes in blood pressure, heart rate and gut motility, there is usually a reflex counteraction or adaptation that attempts to restore the status quo. If the drug is always preceded by the same cues, the adaptive response to the drug will be learned and this will prevent the full manifestation of the drug's effect (tolerance). If the drug is taken under novel circumstances, tolerance is reduced and the drug's effect enhanced.

Tolerance to opioids is characterized by a shortened duration and decreased intensity of the analgesia, euphoria, sedation and other effects caused by depression of the central nervous system, as well as by marked elevation in the average lethal dose.[45]

Animal studies

Tolerance to the antinociceptive effects of opioid drugs is easily demonstrated in animal models.[7,16,102]

In a variety of animal species, using varied nociceptive endpoints, the administration of opioids will evoke a powerful dose-dependent increase in the latency with which the animal will respond to thermal, mechanical and chemical stimuli. Repeated exposure of the animal to the opioid will result in a decrease in the effect produced by a given dose of the drug, in terms of the magnitude of effect or of the duration of action and, where examined, a shift to the right in the dose–response curve.

Studies on animals undergoing continuous opioid infusions by various routes have shown tolerance to be pharmacodynamic, time- and dose-dependent, receptor-specific and apparently reversible if the agonist is removed.[86,88,102]

Recent work in mice has shown that both competitive and non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonists block the development of antinociceptive tolerance to morphine, but not of that to fentanyl nor to a delta selective agonist.[7] This study suggests that there may be significant mechanistic differences between the development of tolerance to morphine (with affinity at mu, delta and kappa receptors) and more selective mu agonists. The indications are that blocking of opioid tolerance by NMDA antagonists is not a general phenomenon but appears selective for tolerance induced by morphine. The potentially significant clinical implications of this have not yet been investigated. The use of ketamine in severe cancer pain uncontrolled by opioid analgesia has been described,[15] and use of this drug in difficult pain problems is increasing.

Morphine self-administration in rats with adjuvant-induced arthritis has been studied in an attempt to evaluate the development of morphine tolerance in a model of chronic pain.[54] Arthritic rats self-injected less morphine than pain-free rats and their dose remained stable over 29 days, in contrast with pain-free rats who escalated their morphine dose. Bolus doses of the anti-inflammatory drug indomethacin early in this study led to reduced morphine intake. However, with the reduction of the adjuvant-induced arthritis, arthritic rats rapidly increased their opioid intake and the administration of indomethacin did not reduce this. The authors postulated that arthritic and pain-free rats self-administer morphine initially for qualitatively different positive reinforcement. The initial positive reinforcement in arthritic rats may be analgesia – hence the dose stability and the reduction seen with administration of indomethacin. As the pain dissipates, the animals in the arthritic group may inject morphine for other positive reinforcing properties, such as euphoria or to prevent withdrawal symptoms. The investigators suggest that the presence of pain has a significant influence on the development of tolerance in these animals.

Colpaert has also postulated that chronic nociceptive stimulation acts to antagonize the apparent tolerance otherwise associated with prolonged opioid administration and proposed the system theory as an alternative model.[18]

Human studies and clinical observations in man

Assessment of the opioid tolerance of patients in pain is constrained by numerous difficulties, and few studies have directly examined the rate of development of tolerance to the analgesic effects of opioids in man.

ACUTE TOLERANCE

Studies on acute tolerance in man have yielded conflicting results. McQuay investigated acute tolerance to fentanyl in a perioperative study. He found no significant difference in postoperative pain, respiratory function and analgesic demands in patients who had received varying doses of perioperative fentanyl and who had significant differences in plasma fentanyl levels. He suggested that this supported the hypothesis of acute tolerance.[58]

In contrast, Inturissi studied the pharmacokinetic–pharmacodynamic relationships of methadone during a brief infusion. Analysis of plasma concentration and analgesia during and after the infusion did not demonstrate a clockwise hysteresis, which would be expected if acute tolerance, or any other process that reduced analgesic efficacy during this brief period, had occurred.[42]

Chapman and Hill studied patients with mucositis in a bone-marrow transplant unit.[13] Marrow transplant is used in the aggressive treatment of malignancies unresponsive to other therapies. High-dose chemoradiotherapy is used before bone-marrow transplant and toxicity from this is unavoidable. The onset of intensely painful mucositis, thinning and breakdown of mucosal tissue and mucosal desquamation is predictable. The condition develops a few days after transplant, intensifies rapidly and remains severe for 1–3 weeks until healing is complete. The pain is most severe in the oral cavity, rendering patients being unable to speak or eat without pain, and opioid analgesics are often needed.

Morphine usage in patients self-administering the drug for 2 weeks was compared with that in patients who received morphine via routine staff-controlled continuous infusion. In both groups, the morphine intake increased steadily over several days as the mucositis worsened and then levelled off. The self-administering group used less morphine overall than the continuous-infusion group. There was no evidence of the development of tolerance in the group who self-administered morphine, whereas the group receiving the continuous infusion needed an increasing amount of drug to maintain the same level of pain control. Withdrawal symptoms did not occur in the self-administering group and this group stopped using morphine sooner than the continuous-infusion group. This study has been replicated with similar results showing no evidence of tolerance, withdrawal or addiction,[39] and suggests that patients do not increase their opioid dose unless there is an increase in pain intensity and that as this reduces, reduced morphine usage follows.

PROLONGED ADMINISTRATION

Houde and colleagues studied tolerance to analgesia in the patient with cancer pain. The analgesic effects of graded doses of morphine on pain relief were studied in 10 patients on two occasions 2 weeks apart; during this interval, patients received morphine analgesia. A clear shift to the right in the dose–response curve indicated a degree of tolerance to the analgesic effects of morphine.[41]

In a study to compare the analgesic activities of diamorphine and hydromorphine, a relatively smaller analgesic response to these drugs was associated with a greater degree of opioid consumption in the 48 h before the start of the study.[96]

Cancer pain

Foley has written extensively on opioid tolerance in the cancer patient and critically addressed the extent to which tolerance limits the patient's ability to obtain adequate analgesia from opioid therapy during their illness.[27–29] She describes three patterns of drug use: (1) rapidly escalating doses of opioids, associated with escalating pain, anxiety or both; (2) stable doses of opioids, for periods of weeks or months, without dose escalation and reduction; and (3) discontinuance of opioid drugs with effective analgesia from anticancer therapies, neurolytic nerve block or neurosurgical procedures. These patterns have been described in outpatients, inpatients, in a group of patients with terminal illness,[19 20 49] and also in a group of patients with non-malignant pain.[71]

Many other studies have shown that most cancer patients with severe pain, taking opioids by a variety of routes, have long periods (weeks, months or years) of stable opioid dose.[5 8 34 83 92] In addition, Plummer has demonstrated poor correlation between the ratio of maximum dose/minimum dose (a measure of dose escalation) and the duration of extradural analgesia in a group of cancer and non-cancer patients. In fact, the morphine dose was more stable in patients with chronic non-malignant pain than in the cancer patients, suggesting that increasing nociceptive stimulus was the major influence on opioid dose.[70]

While it is generally agreed that tolerance to opiate analgesia occurs, it does not appear to be a limiting factor. Dose escalation is considered to be predominantly a consequence of increasing pain as a result of increasing nociceptive input as the disease progresses.[17 19 20 28 29 49 83 92]

Table 2 A 'differential diagnosis' for declining analgesia in the clinical setting (adapted from reference 74)

- Increased activity in nociceptive pathways
  - Increasing activation of nociceptors in the periphery because of
    - mechanical factors (e.g. tumour growth)
    - biochemical changes (e.g. inflammation)
    - peripheral neuropathic processes (e.g. neuroma formation)
  - Increased activity in central nociceptive pathways, because of central neuropathic processes (e.g. sensitization, shift in receptive fields, change in modulatory processes)
- Psychological processes
  - Increasing psychological distress (e.g. anxiety, depression)
  - Change in cognitive state leading to altered pain perception or reporting (e.g. delirium)
  - Conditioned pain behaviour independent of the drug
- Tolerance

Portenoy has elaborated on other major factors that are important for declining analgesia in the patient with cancer pain, and produced a "differential diagnosis"(table 2).[74]

Increasing nociceptive input may occur with disease progession. It may also occur with inflammation and with the development of peripheral or central neuropathic processes (for example, neuroma formation or expansion of receptive fields). Psychological processes, such as anxiety or depression, and alteration in cognitive state (for example, delirium[21]) can also lead to worsening pain. Humans present a complex interplay of processes, and pain reporting can also change as a reaction to the responses of "significant others".

Portenoy concludes that loss of analgesic effects cannot be attributed to pharmacodynamic tolerance unless an alternative explanation for increasing pain cannot be found.

It has also been suggested that tolerance-like problems are more commonly seen in patients who have pain that appears to be relatively resistant to opioids.[4] The nature of opioid responsiveness is controversial.[24] There are two extremes of opinion. One view is that opioid responsiveness is a relative phenomenon, and that any pain can be controlled by opioids provided there is an adequate dose and control of adverse effects.[72] At the other extreme, some investigators believe that the lack of response can be predicted from the clinical characteristics of the pain. Nociceptive pain is thought to be responsive to opioids, whereas neuropathic pain is regarded as non-responsive.[4 6 51 52] However, recent studies have shown that pain judged to be neuropathic may be responsive to opioids, although it is generally less so than nociceptive pain.[44 61]

Portenoy has proposed that opioid responsiveness is a continuum of responses, that can be defined operationally as the degree of analgesia obtained after upward dose titration to an end-point defined by analgesia or by the onset of intolerable and unmanageable side effects. Implicit in his conceptualization is the view that both patient-related and pain-related factors are important.[72]

A validation study of the Edmonton staging system for cancer pain was able to identify patients who were relatively less likely to attain satisfactory analgesia during opioid therapy.[10] Features of these patients were an inferred neuropathic aetiology for the pain, the presence of incident pain, impaired cognitive function, major psychological distress, a high initial opioid dose, a rapid increase in opioid dosage (more than 5% of the initial dose per day) and a history of alcoholism or drug abuse.

The pragmatic response of the clinician when the analgesic effect of the opioid becomes inadequate is to increase the dose. This is satisfactory if: (1) the dose given is sufficient to overcome the factors that have reduced the analgesic effects of the agent; (2) side effects do not limit the dose of drug that can be given; or (3) if the pathological substrate that mediates the pain remains opioid sensitive. A two- to 10-fold increase in dose may be necessary to achieve analgesia because the dose–effect relationship is based on a log dose concentration. As Foley has stated "the dose that works is the dose that works".[29]

Non-cancer pain

A continual increase in nociceptive focus is less likely in patients with non-malignant pain than those with cancer. Patients with non-cancer pain have demonstrated more stable morphine dosage that those with pain of malignant origin.[70] Penn has shown that tolerance to intrathecal morphine in non-malignant pain was not a problem and in his series dose increase was also related to increasing pathology.[69] Clinical surveys concerning the long-term use of opioids in patients with non-malignant pain are more limited than those in cancer patients, but have not shown the development of tolerance to be a clinical problem.[30,68,69,70,89,91,93,104]

More objective data indicate that the minimum effective analgesic blood concentration of pethidine did not change significantly when measured over time (3–12 months) in three patients with chronic pain, and was independent of the route of administration.[33]

SELECTIVE TOLERANCE

Various studies and clinical experience suggest that tolerance to different opioid side effects develop at different rates and this has been termed 'selective tolerance'.[89]

Initial manifestations of opioid administration in most individuals are analgesia, sedation, nausea and vomiting, respiratory depression, pupillary constriction, constipation and euphoria or dysphoria. Tolerance to nausea and vomiting, sedation, euphoria and respiratory depression occur rapidly, while tolerance to constipation and miosis is minimal.[9,50,53,67]

Constipation

Constipation is the most common adverse effect of opioid analgesics when they are used for chronic cancer pain. Opioid analgesics bind directly to peripheral opioid receptors in the gastrointestinal tract, causing decreased peristalsis, diminished biliary, pancreatic and intestinal secretions and increased ileocaecal and anal sphincter tone. Stool transit time increases and desiccation of faeces results. If the clinical effect is sufficiently severe, opioids can produce narcotic bowel syndrome, which is characterised by nausea and vomiting, mild abdominal discomfort, constipation, gaseous abdominal distention and functional colonic obstruction.[81] As tolerance to constipation develops very slowly or not at all, constipation must be anticipated and treated prophylactically with adequate laxatives.

The development of tolerance to emesis and sedation is clinically apparent and obviously beneficial to the patient.

Nausea

Nausea has been estimated to occur in up to 40% and vomiting in 15% of ambulatory patients treated with opioids. In many patients it is an initiation side effect and resolves after a few days. As most patients will not develop nausea and vomiting while taking opioids, prophylactic antiemetic treatment is not usually indicated.

However, when patients are first prescribed opioids they should have ready access to antiemetics if these side effects occur. Then, the opioid and anti-emetic regimen should be concurrently administered in a regular fashion for 4–7 days. After this time, tolerance to emetic effects of opioids usually develops and the antiemetics can gradually be withdrawn. Patients may err by taking analgesia and antiemetics sporadically rather than regularly. Intermittent use in this way can impair the development of tolerance to this side effect, and patients should be advised accordingly.

Sedation

Sedation and cognitive impairment can be demonstrated during the administration of opioid analgesics by various routes.[84] Impaired concentration has resulted in sub-optimal treatment for pain when patient-controlled analgesia (PCA) has been used for severe mucositis.[13]

However, tolerance to the sedative and cognitive effects of opioid analgesics usually develops rapidly, and these side effects are again most problematic at the start of treatment or when the dose is increased. Bruera showed that patients experience significant cognitive impairment after a recent increase in the dose of opiates but patients on a stable dose of opiate showed no evidence of cognitive impairment, thus suggesting that tolerance develops to cognitive effects.[9] This study also suggested that patients were less aware of cognitive impairment than other opioid-induced symptoms. Consideration needs to be given to these findings when patients request advice on driving, working and decision-making while taking opioid analgesics.

However, if sedation persists and pain control is adequate, a 10–25% reduction in dose or continuation of the same dose administered in smaller but more frequent boluses may lessen this side effect. Alternatively, the administration of oral methylphenidate on wakening and at midday is effective and safe in reducing sedative opioid effects.[11]

Respiratory depression

All opioid agonists have similar depressant effects on the brain-stem respiratory centre and respiratory depression is potentially the most serious adverse effect of opioids.

In man, death from overdose of an opioid is nearly always the result of respiratory arrest. When respiratory depression occurs as a result of opioid administration, it is usually in opioid-naïve patients after acute administration of an opioid; it is associated with other signs of central nervous system depression, including sedation and mental clouding.

Tolerance appears to develop rapidly to respiratory depression with repeated drug administration, allowing opioid analgesics to be used in the management of chronic cancer pain without significant risk of respiratory depression.

However, pain acts as an antagonist to the central nervous system depressant and in particular to the respiratory depressant effects of opioids.[36 37 59 60] McQuay has postulated that the respiratory centre in the medulla might receive nociceptive input.[59] Particular care is indicated in the continued management of patients receiving high doses of opioid who undergo a neurolytic or neurosurgical procedure that abruptly reduces nociceptive input. Removal of the stimulatory effect of the pain may lead to an unopposed opioid-mediated respiratory depressant effect, and may result in somnolence or respiratory depression.[36 37] In the case of a successful neuroablative procedure, the dose of opioid should be tapered and the patient carefully observed.

Opioid-induced respiratory depression is infrequent. Doctors' and nurses' inordinate fear of this complication is an important impediment to adequate control of cancer pain.

CROSS-TOLERANCE

Repeated doses of a drug in a given category confer tolerance not only to the drug being used but also to other drugs in the same structural and mechanistic category[67]; this effect is known as cross-tolerance.

Animal studies have shown cross-tolerance to be incomplete.[43 64 66 88] Neil demonstrated that mice pretreated with morphine were tolerant to morphine only, while methadone-treated mice were tolerant to methadone, morphine, codeine and D-propoxyphene and more so to morphine than to methadone itself.[66] Evidence suggests that incomplete cross-tolerance results from selective tolerance at different subpopulations of opioid receptors. It has been shown that a mu-selective drug induces only minimal tolerance at kappa or delta receptors.[88] Moulin has shown that rats chronically infused with levorphanol (an agonist at mu, kappa and delta receptors) develop substantial cross-tolerance to the analgesic effects produced by a dose of morphine (a relatively selective mu agonist), whereas rats infused with morphine demonstrate little tolerance when challenged with a dose of levorphanol.[64] This raises the possibility that there is clinical advantage in using morphine before levorphanol in the management of severe pain and indicates the need for controlled clinical studies to determine whether patterns of cross-tolerance between commonly used opioid drugs could dictate the sequence in which they should be used.

The patterns of cross tolerance to various opioids exhibited by patients are unpredictable, but appear to be incomplete.[25] Patients who have pain uncontrolled by morphine in spite of intolerable side effects may be switched to an alternative opioid that allows pain control to be achieved without disabling side effects.[1 12 26 31]

Table 3 Symptoms and signs of opioid withdrawal

Symptoms	Signs
Craving for opioids	Pupillary dilatation
Restlessness	Sweating
Irritability	Piloerection
Increased sensitivity to pain	Tachycardia
Nausea	Vomiting
Abdominal cramps	Diarrhoea
Myalgia	Hypertension
Dysphoria	Yawning
Insomnia	Fever
Anxiety	Rhinorrhoea

The variability in response to different opioid drugs has important clinical implications. It has been suggested that in difficult pain problems, when dose escalation with morphine or any other opioid yields intolerable side effects, sequential drug trials may identify an opioid that provides the favourable balance between analgesia and side effects.

PHYSICAL DEPENDENCE

Physical dependence is defined as the potential for an abstinence syndrome, or withdrawal, after abrupt dose reduction, discontinuation of the drug or administration of an antagonist drug.[45]

Physical dependence and withdrawal symptoms have been extensively studied and described in animals[56 78] and in man[22 53] (table 3).

In the clinical setting, the lowest dose and shortest duration of treatment that may predispose to a significant abstinence syndrome is not known. Physical dependence probably starts with the first dose of an opioid drug and should be presumed to exist if opioids are given repeatedly for a few days. However, patients who receive therapeutic doses of morphine several times a day for 1–2 weeks will have only mild withdrawal symptoms that may not be recognized as such when the drug is stopped. Symptoms are even less pronounced when the drug is one that is slowly eliminated, such as methadone. However, by administering naloxone, an opioid antagonist, withdrawal symptoms can be precipitated after only one or two therapeutic doses of morphine, even in individuals who have no prior history of opioid dependence.[46]

The prevention of unpleasant withdrawal symptoms has been suggested as a positive reinforcer for continued morphine self-administration in animals.[54] The fear of withdrawal has been considered to be one of the major forces behind persistent drug abuse in addicts.

Neither the prevalence nor the pattern of opioid withdrawal has been systematically studied in patients with pain. In the cancer population, effort is usually made to reduce opioid dose slowly in patients whose pain has been relieved by alternative methods, such as neurolytic block or radiotherapy, and with this practice withdrawal symptoms do not appear to be a problem. However, abrupt cessation of opioids or administration of opioid antagonists in this situation can result in classical withdrawal symptoms, which can be controlled by the resumption of low-dose opioids.[37 49]

In a population with chronic non-cancer pain undergoing opiate reduction during an inpatient pain-management programme, withdrawal symptoms were not recorded as problematic.[77]

The implications are that although patients who take long-term opioids may become physically dependent (and thus display an abstinence syndrome if the dose is abruptly decreased or an antagonist given), reduction and subsequent discontinuation can occur without adverse effects if the dose is tapered slowly.

ADDICTION

Standard definitions of addiction have been developed from experience with substance abusers and must be cautiously interpreted when applied to patients who are receiving a potential drug of abuse prescribed for an appropriate medical indication.

Addiction has been defined as "a behavioural pattern of drug use, characterized by overwhelming involvement with the use of a drug (compulsive use), the securing of its supply, and the high tendency to relapse after withdrawal".[45]

A task force of the Panels on Alcoholism and Drug Abuse of the American Medical Association (AMA) Council on Scientific Affairs formulated the following definitions:

Addiction: "a chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological or social harm to the user and continued use despite that harm".[79]

Addict: a person who is physically dependent on one or more psychoactive substances, whose long-term use has produced tolerance, who has lost control over his intake, and would manifest withdrawal phenomenon if discontinuance were to occur.

Although the AMA Task Force decided to include the finding of physical dependence in the definition of an addict, the criteria for the latter still include the loss of personal control over drug use; the Task Force is thereby proposing a distinction between the addict and the physically dependent patient. Both these definitions emphasize that the development of addiction is a psychological and behavioural process.

Opioid pseudoaddiction

Pseudoaddiction has been used to describe the iatrogenic syndrome of behavioural changes similar to those seen with idiopathic opioid addiction that can develop as a direct result of inadequate pain management.[98]

Uncontrolled pain from both malignant and non-malignant causes (such as sickle-cell crisis, tuberculosis) combined with inadequate analgesia can result in increasing demands and bizarre drug-seeking behaviour by the patient. The patient feels angry and emotionally isolated from the health care team, who in turn try to avoid contact with the patient because of frequent pain complaints and demands for analgesia. These patients are often described as 'clock watchers'. A vicious cycle of anger, isolation, and avoidance lead to complete mistrust. The importance of recognizing this syndrome cannot be over-emphasized. Treatment strategies start by acknowledgement that the pain is real and the establishment of trust between the patient and the health care team. Appropriate and timely analgesia to control the patient's pain then needs to be prescribed and given using scheduled rather than 'as required' dosing, with additional medication for breakthrough pain and frequent re-evaluation.

There is ample support both from animal studies and from observation of human addicts for the proposition that opioids are inherently reinforcing drugs. Addicts usually report euphoric effects from opioid drugs and it is thought to be this and the avoidance of the aversive effects of withdrawal that are involved in the pathogenesis of addiction. In contrast, administration of opioids to human volunteers and patients can produce dysphoria and not a consistent euphoria.[46]

Although an improvement in mood has been demonstrated in post-operative cancer patients following the administration of morphine and diamorphine, this coincided with relief of pain.[46,48]

Addiction has been shown to be more complex than just the result of repeated exposure to a drug. There was a high prevalence of opioid addiction among US soldiers in Vietnam; however, surveys of returning veterans demonstrated that a large proportion of those who abused heroin stopped this activity abruptly on return to a normal life in the US and that the relapse rate was low.[80] In sharp contrast, a group who underwent a 6-month inpatient treatment programme under the Narcotic Addict Rehabilitation Act were readdicted within 6 months of their release.

Addiction in patients with chronic pain

Two early surveys (in 1925 and 1939) of addicts undergoing treatment reported that 9% and 4% respectively began their addiction with a medical prescription of an opioid drug for a painful disorder.[73] In 1954, a report noted that 27% of white male addicts and 1.2% of black male addicts began abuse as medical patients treated for pain.[73] Surveys of addicted populations are clearly subject to bias and a different view has emerged from more recent data on medical patients who were assessed for the development of addiction after receiving opioids for the treatment of pain.

The Boston Collaborative Drug Surveillance Programme reported only four cases of well documented addiction in 11 882 hospitalized patients with no previous history of addiction who had received opioids.[76]

Furthermore, abnormal drug-seeking behaviour was not seen when long-term opioids were used for postherpetic neuralgia,[68] phantom limb pain,[93] chronic spinal pain[30] and pain of mixed but well defined origin.[91] Taub described 313 personally treated patients with intractable pain who were maintained on opioid analgesics for up to 6 years. Only 13 patients presented serious management problems, and each of them had a history of substance abuse (opiates or alcohol).[89] Portenoy also identified this risk factor in his study of 38 patients treated with opioids for non-malignant pain; the two patients who required escalating doses of opioids each had a history of drug abuse.[71]

However, Maruta found that 65% of 144 consecutive patients referred for chronic non-malignant pain management were abusing or dependent on (using their definition) weak and strong opioid drugs and had a strong family history of alcohol abuse.[57]

Therefore, clinical experience suggests that there may be a spectrum of responses to pain in patients treated with opioids, ranging from appropriate and acceptable drug-seeking in patients with unrelieved pain to a group of clearly pathological responses that can occur even in those with severe pain. Most of the patients who developed drug-seeking behaviour had a prior problem with illicit drug abuse.

Redefinition of addiction in patients taking opioids for chronic pain

Portenoy has suggested redefining addiction in patients taking opioids for chronic pain as follows: "a psychologic and behavioural syndrome characterized by: (1) an intense desire for the drug and overwhelming concern about its continued availability (psychologic dependence); (2) evidence of compulsive drug use (characterized, for example, by unsanctioned dose escalation, continued dosing despite significant side-effects, use of drug to treat symptoms not targeted by therapy, or unapproved use during periods of no symptoms); and/or (3) evidence of one or more of a group of associated behaviours, including manipulation of the treating physician or medical system for the purposes of obtaining additional drug (altering prescriptions, for example), acquisition of drugs from other medical sources or from a non-medical source, drug hoarding or sales, or unapproved use of other drugs (particularly alcohol or other sedatives/hypnotics) during opioid therapy."[73]

USE OF OPIOIDS IN NON-MALIGNANT PAIN

The long-term use of opioid analgesics for the treatment of chronic non-malignant pain is controversial. The possibility of rapid dose escalation as a result of tolerance and the development of physical dependence, addiction and increasing disability have been major concerns.[57 82] However, clinical experience demonstrates that some patients with chronic pain derive benefit from opioids.[30 71 89 91 93 104]

Current opinion is that there is a small group of patients with chronic non-malignant pain who may benefit from long-term opioid therapy. Guidelines have been produced to assist in the assessment, selection and subsequent management of patients who might be considered suitable for long-term opioid therapy.[35 62 73 75 90]

OPIOPHOBIA

Opiophobia is the phenomenon of failure to administer legitimate opioid analgesics because of a fear of the power of these drugs to produce addiction.[63]

Underutilization of opioid drugs in acute and cancer pain results in unnecessary suffering.[2 63 106] The major reasons for this underuse are overestimation of the risks of opioid toxicity, intense concern among health care professionals, patients and their families about addiction and tolerance, legal sanctions that impede the prescription of opioid drugs to those who need them and a lack of systematic education. Undertreatment (in terms of both prescription and administration) also occurs because of custom and culture. Individuals perceived to be at greater risk of addiction, such as those who belong to the lower socioeconomic groups, the young and non-white patients may receive less opioids.[63] Zenz has eloquently rebutted the "morphine myths" relating to sedation, addiction and tolerance.[105] He has highlighted the overemphasis on the potential hazards of opioids, and calls for better education to reduce prejudice against their proper use.

Opioid tolerance in children

The development of opioid tolerance in children is variable and depends on the clinical context. When opioids are used to treat cancer pain in children, tolerance appears to develop quite slowly and, in most cases, dose escalation is caused by spread of disease rather than tolerance per se. The dose can be increased as in the adult patient to obtain pain relief, and dose increases are limited only by the occurrence of unmanageable side effects. The effective dose of a strong opioid will vary widely from child to child. Some patients will require a high dose to achieve pain relief.

As in adult patients, cross tolerance between opioids is incomplete. It is suggested that, if it is necessary to switch from one strong opioid to another, half the generally accepted conversion dose should be used initially, followed by upward titration as needed. Tolerance to opioids appears to be rapidly reversible once administration is discontinued. Therefore, if the child has a history of requiring massive doses of opioids previously, but has recently had a drug-free interval, standard opioid doses should be used initially with escalation as necessary.

There is no evidence that preadolescent or adolescent children are at a higher risk of developing addiction or psychological dependence than the general population when given opioids for the management of pain.

However, in newborns receiving opioids to help them endure mechanical ventilation and extracorporeal membrane oxygenation, the development of opioid tolerance does appears to be problematic.[101] Fentanyl may produce tolerance more rapidly than morphine. In addition, it appears that tolerance will develop more rapidly if the opioid infusion is continuous rather than intermittent. Work is ongoing to ascertain whether tolerance is different in the neonate and to elucidate the factors influencing the development of tolerance in this group of patients.

Case report

The following case report illustrates many of the points about tolerance discussed in this review.

In 1988, a 52-year-old man was diagnosed with multiple myeloma and underwent conventional therapy for his disease. In 1992, he presented with pain in his right groin and X-ray examination revealed a myelomatous deposit in his right pubic ramus. Nausea and vomiting precluded morphine analgesia for the pain, which was subsequently relieved by radiotherapy.

In March 1993, the patient developed back pain and further myelomatous deposits were discovered. He began oral morphine 10 mg 4-hly; radiotherapy achieved little reduction in his pain and his medication was changed to sustained-release morphine 120 mg daily, with 10 mg immediate-release morphine for breakthrough pain. An episode of sepsis increased his morphine requirements to 160 mg daily. When this was treated with antibiotics, he reduced the dose again to 120 mg daily.

From May 1993 until August 1994, the patient's oral morphine dose was stable at 140 mg daily. Tolerance to analgesia was not clinically apparent. During this period, he required multiple laxative therapy and one inpatient admission for constipation.

In August 1994, he developed pain in his cervical and lumbar spine, occipital neuralgia and severe leg pain. Disease progression was confirmed by a rise in plasma light-chain levels and X-rays revealed a fracture of the spinous process of his second cervical vertebra and further deposits in his lumbar spine. Radiotherapy was helpful for the cervical pain but not the leg pain, which was relieved by an extradural steroid injection.

In April 1995, the patient developed pain in the lumbar region and down his left leg. Further lytic lesions were noted in his 4th lumbar vertebra, his left hemipelvis and his left femur. His morphine requirements rose to 800 mg per day. He underwent radiotherapy and started amitriptyline, with only moderate relief of his symptoms. In May 1995, a second extradural steroid injection was given. Three days after this, he had only minimal rest pain, though some incident pain, and had reduced his morphine to 120 mg per day with no obvious withdrawal symptoms. In July 1995, he developed a further lytic lesion in his right ilium. Temporarily his morphine intake rose to 1000 mg per day. After successful radiotherapy, he reduced this to 160 mg. Figure 1 illustrates the patient's morphine intake over the period described.

At the end of September 1995, he was admitted to hospital with increasing pain. His dose of morphine was rapidly increased. He became confused and developed myoclonic jerks. Investigations revealed pneumonia and acute renal failure, which were treated. The patient complained of increasingly severe pain in his back and right thigh in spite of increasing doses of s.c. diamorphine (600 mg per day) and midazolam, additional oral and i.v. morphine, oral non-steroidal anti-inflammatory drugs and other coanalgesic drugs.

It was decided to insert an extradural catheter and begin an infusion of diamorphine and bupivacaine. An extradural catheter was inserted at the level of L2/3 and the position verified with contrast medium. Following a bolus dose of bupivacaine 0.5% plain 10 ml, there was an immediate improvement in the patient's pain and no cardiovascular instability. An infusion of diamorphine and bupivacaine 0.25% plain was started. Twelve hours later, he became hypotensive (systolic blood pressure 70 mm Hg) and sensation to light touch was reduced up to the T9 dermatome. Cerebrospinal fluid was aspirated from the catheter. The infusion was altered to deliver diamorphine 4 mg in 4.8 ml bupivacaine 0.25% plain in 24 h and the next day an MRI scan was performed (Figure 2). This showed widespread bony metastatic disease and a large soft tissue mass arising from the lower thoracic vertebrae, destroying the vertebral bodies and encroaching on the spinal cord. The epidural catheter was noted to pass through the tumour and into the thecal sac.

Over the next 4 days the infusion needed to be increased to diamorphine 8 mg and bupivacaine 7.2 ml 0.25% plain over 24 h. Although the pain was controlled while the patient lay in bed, incident pain in his lumbar spine prevented any movement. Additional oral morphine, intrathecal clonidine (150 g/24 h), intrathecal midazolam (5 mg/24 h), s.c. salmon calcitonin and s.c. ketorolac (90 mg/24 h) was of no benefit. The incident pain could be improved by 1 ml bolus doses of intrathecal bupivacaine, which made the patient totally immobile but gave great relief.

An orthopaedic opinion was sought and the patient underwent spinal fixation from T6 to S1. After the operation his pain was managed by combined s.c. infusion of diamorphine 800 mg and midazolam 20 mg and a separate infusion of ketorolac 90 mg per day. Gradually his mobility improved and he was able to sit and transfer from bed to chair. On discharge home his daily oral morphine dose was 2.5 g.

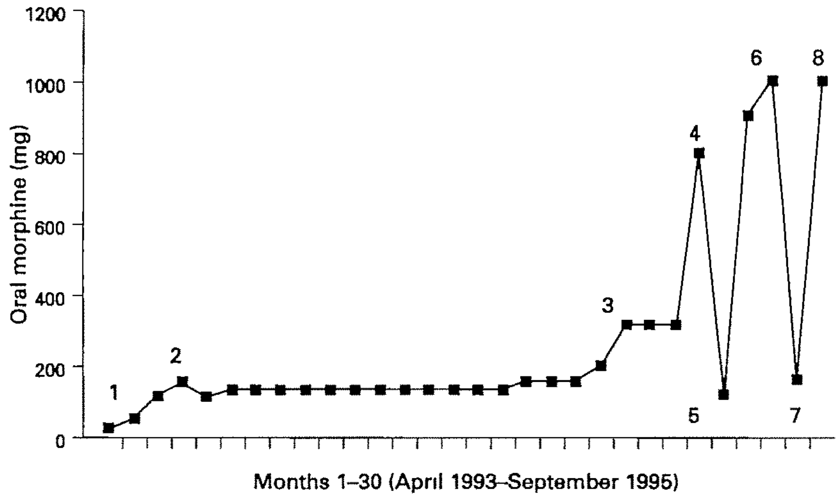

Figure 1 Daily morphine requirements (May 1993–September 1995) of a man diagnosed with multiple myeloma in 1988, at the age of 52 years. 1 = onset of pain; 2 = septic episode; 3 = disease progression (x-ray and haematological confirmation); 4 = disease progression; 5 = radiotherapy, steroid extradural injection, coanalgesics; 6 = disease progression; 7 = radiotherapy; 8 = disease progression.

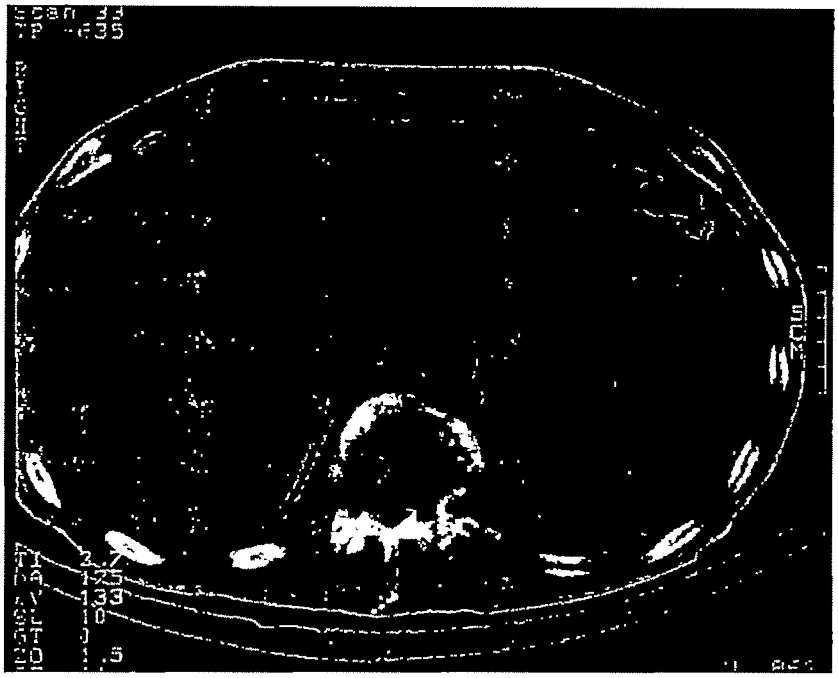

Figure 2 MRI scan of a man being treated for severe pain in the late stages of multiple myeloma. Note the extensive bone and soft tissue myelomatous disease and an extradural catheter passing through the tumour into the thecal sac.

However, he returned to the ward complaining of increasing incident pain in his lumbar spine and down his right leg. It was decided to substitute methadone for morphine. Methadone 60 mg four times daily was prescribed, with additional immediate-release oral morphine for his incident pain. Without doubt, his pain was significantly better controlled with methadone than it had been with morphine. Methadone was reduced to 60 mg three times daily and then to 150 mg per day and he needed little extra oral morphine for incident pain. He described his pain control as excellent.

Two months later, the patient's condition deteriorated and he was not able to take oral medication. A s.c. infusion of methadone (initially 50 mg/24 h, increased to 120 mg/24 h) gave good analgesia for the last 3 days of his life.

Conclusion

Tolerance to opioids has been clearly demonstrated in animal studies and the phenomenon occurs in humans with respect to both the analgesic and non-analgesic effects of these drugs.

In clinical practice, analgesic tolerance is rarely a limiting factor during opioid therapy. Concern about tolerance does not justify delay in starting opioid therapy nor should it limit dose escalation in a patient with cancer pain. Patients and their families should be reassured that tolerance to opioid analgesia is not a clinical problem and that morphine will continue to relieve their pain for many months or years. Worsening pain occurring in a patient previously on a stable dose of opioid should never be attributed to the development of tolerance unless comprehensive evaluation fails to reveal an alternative explanation.

Prevention of the development of tolerance by NMDA antagonists and the recognition that there is incomplete cross-tolerance to both the analgesic and non-analgesic effects of opioids have important potential clinical implications. The pre-eminent question – whether the very presence of pain has some modulatory effect on the development of tolerance – has yet to be answered.

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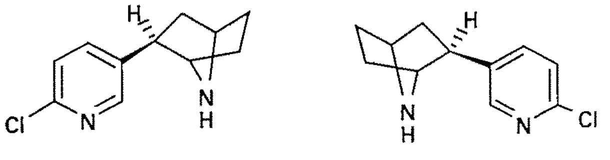
Epibatidine and pain

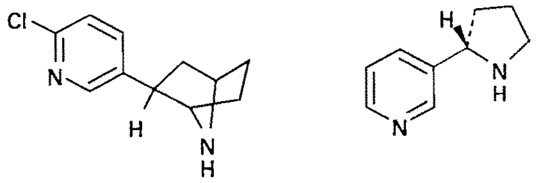
J. R. TRAYNOR

In 1992 the chemical epibatidine (fig. 1), isolated from the skin of the Equadorian poison-arrow frog *Epipedobates tricolor*, was shown to be 200 times more potent than morphine in blocking heat nociception in the mouse. The study was carried out using the hotplate test, which measures the time taken for a mouse to show a behavioural response (jumping or paw licking) when stood on a heated plate maintained at 55°C.[63] Epibatidine had been described 10 years earlier by Daly and colleagues at the National Institutes of Health, Bethesda, USA, but had been isolated in such small amounts that it could not be characterized. However, so potent was the antinociceptive effect of the compound – less than 5 μg kg^{-1} i.p. causes an antinociception response in the mouse – that the effect was used as a bioassay during the further isolation and purification of epibatidine. The antinociceptive effect of epibatidine was not blocked by the opioid antagonist naloxone, suggesting a therapeutic action different from that of morphine and a potentially novel therapeutic mechanism of providing pain relief. This was an exciting finding because it opened up the possibility of a new therapy, without the adverse effects of opiates, for the treatment of severe pain. However, epibatidine was extremely toxic, causing hypertension, respiratory paralysis and seizures, with death occurring at doses not much higher than those required for antinociception.[11,65] Extensive modification of the compound would be necessary to provide a useful therapeutic agent. Such was the interest in epibatidine that by 1993 synthetic material was available in larger amounts.[14,36] Synthesis of the optical isomers of epibatidine quickly followed,[28] potentially offering an important advantage in describing the pharmacology of the compound. Epibatidine is the exo-isomer of the two possible geometric isomers (fig. 1) and can exist as two enantiomers (+)- or R-epibatidine and (–)- or S-epibatidine. The natural compound is the (+) isomer,[72] although there is little difference in pharmacological activity between the (+) and (–) isomers.[6,20,72] The endo-isomer (fig. 1) is inactive.[27,58] These advances in synthesis of epibatidine's isomers made it possible to discover more about this exceptionally potent compound.

A news article in *Science* in 1993[12] stated that the "race is on to turn the potential (of epibatidine) into reality". In this review, I shall consider the progress that has been made towards realizing this goal, including the development of less toxic analogues, such as ABT-594, that retain a wide spectrum of antinociceptive actions.[9]



(+)-Epibatidine (–)-Epibatidine



Endo-epibatidine (–)-Nicotine

Figure 1 Structure of epibatidine isomers.

Epibatidine and analgesia

ANTINOCICEPTION

In spite of the high level of interest in this compound, the antinociceptive activity of epibatidine has been investigated only in rodents. The effect of epibatidine was originally observed in the hotplate assay, where at 2.5 μg kg^{-1} i.p. the compound causes significant hotplate "analgesia".[63] This compares with a value of approximately 10 mg kg^{-1} for morphine in the same test. Most studies on this compound have used a similar hotplate technique[6,10,58,65] (fig. 2) but a further heat nociceptive test, the tail-flick test, which measures latency to removal of the tail from a radiant light source, has also been used.[6,21,56] Other tests applied have been footshock, where the nociceptive stimulus is an electric current and the end point is vocalization,[11] and carrageenan-induced hyperalgesia in the rat hindpaw.[58] In all these experimental paradigms epibatidine is approximately equi-active and equi-efficacious with morphine (fig. 2), except in the footshock vocalization assay, where it was observed to be less efficacious. There have been no reports of the

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use of epibatidine as an antinociceptive agent in non-human primates or as an analgesic agent in humans, presumably because of its low margin of safety.

Mode of action

The original reports on epibatidine showed that the antinociceptive action of the compound was not reversed by naloxone, although in mice the drug elicited a Straub tail response; this response is customarily used as a indicator of morphine-like action, that is, activation of µ-opioid receptors. However, synthetic (+)- and (−)-epibatidine do not produce a Straub tail response,[11,58] suggesting that the observation with the natural material may be a toxic syndrome produced by high doses, or attributable to other substance(s) present in the frog skin extracts. Furthermore, a Straub tail response is induced in mice by several other drugs, including agonists acting at nicotinic and 5-hydroxytryptamine (5-HT) receptors. Thus, there is no pharmacological evidence for an opioid mechanism of action for epibatidine and in confirmation of this there are numerous reports that the compound does not bind to opioid receptors.[6,56,58,65] In fact, the compound shows no affinity for a variety of neuronal receptors including benzodiazepine, serotonergic, dopaminergic, adrenergic and $GABA_A$ receptors, and receptors for bradykinin, CCK, excitatory amino acids, CGRP and neurokinin.[6,56,58,65] Epibatidine does have low affinity for the muscarinic acetylcholine receptor but its binding profile suggests antagonist action at this site.[58]

On the other hand, the similarity of the structure of epibatidine (fig. 1) to that of nicotine was soon recognized and it was subsequently demonstrated that the compound has high affinity for nicotinic acetylcholine receptor (nAChR) binding sites labelled by [^{3}H]nicotine or its derivatives.[6,56,58,65] Nicotine has long been recognized to be active in tests for antinociception,[46] although its low activity and poor side-effect profile precluded any further development. The antinociceptive actions of nicotine are prevented by the nicotinic cholinergic receptor channel blocker mecamylamine, but not by the ganglion blocker hexamethonium, which does not pass into the central nervous system; this suggests a central mechanism of action.[1,60,67] In confirmation of this, the quaternary methiodide derivative of nicotine is inactive after s.c. administration but active after i.c.v. administration.[1] Direct injection of nicotine into the central nervous system enhances potency when compared with peripheral administration,[38,60] and antinociception correlates with nicotine concentration in mouse brain.[67]

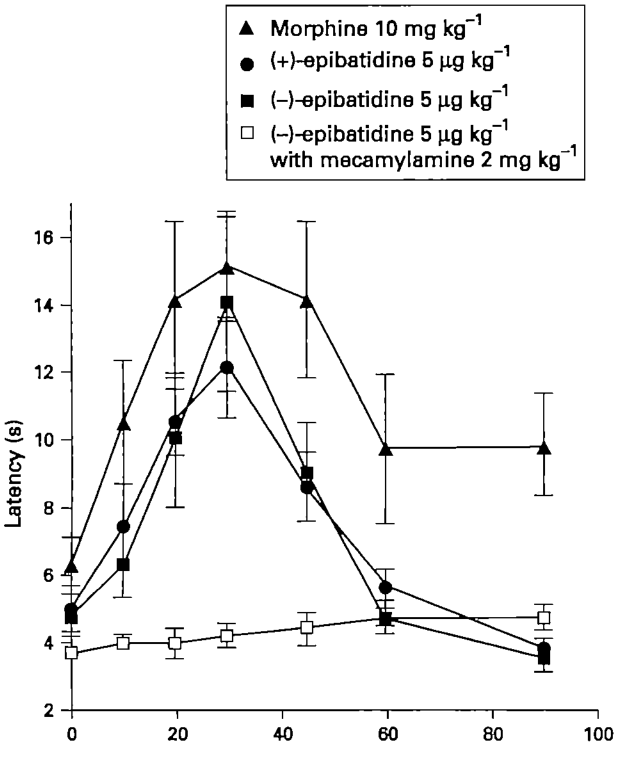


Figure 2 Antinociceptive effects in the mouse hotplate test, measured as time to appearance of the first behavioural response. All drugs were administered i.p. Figure drawn from data in reference 6.

The antinociceptive properties of epibatidine are remarkably similar to those of nicotine in most respects. Antinociception elicited by epibatidine is prevented by mecamylamine,[8,10,11,20,56–58,65] but not by hexamethonium.[20,56] There is one report that hexamethonium partially blocks the action of epibatidine in the tail-flick assay in the rat,[57] which indicates a possible peripheral component in addition to a central component; caution should be used in this interpretation, however, as quaternary compounds like hexamethonium may cross the blood–brain barrier in sufficient amounts to act centrally.[5,24]

Although epibatidine has qualitatively similar antinociceptive properties to those of nicotine, it does show some differences. Whereas nicotine exhibits tolerance to its antinociceptive action after acute or chronic administration, there is no substantial tolerance developed to epibatidine, at least in mice.[21] In addition, epibatidine is considerably more potent. In the various antinociceptive tests carried out in rodents, epibatidine is effective as an antinociceptive agent at approximately 5 µg kg^{-1}; nicotine is approximately 200–300 times less potent, given by various routes,[6,20,56–58] and morphine is approximately 1000 times less potent. The antinociceptive effect of both epibatidine and nicotine is rapid in onset (3–5 min) but whereas the action of nicotine is short-lived (10 min) the effect of epibatidine lasts up to 1 h.[10,56] Epibatidine readily enters the brain after tail-vein administration in the mouse, with high levels in the thalamus and superior colliculus. Maximum concentrations are attained at 30 min and epibatidine is still present at 4 h, showing slow clearance from the brain.[42] This does not appear to relate to the rapid onset and relatively short duration of action reported by several groups. Indeed, after direct central (i.c.v.) administration higher concentrations of epibatidine are required than when the compound is given peripherally (s.c.).[58] On the other hand epibatidine also shows an antinociceptive response after intrathecal administration at the same doses that are active after s.c. administration.[20,40] This may indicate a mechanism of action primarily at the spinal level. However, supraspinal activation of descending inhibitory pathways is a common mechanism for blocking pain transmission at the spinal level and so preventing impulses reaching higher centres. The presence of a central nicotinic cholinergic pathway that modulates antinociception by activation of descending inhibitory pathways has been proposed. At the spinal level this seems to involve α-adrenergic and serotenergic as well as cholinergic systems.[37] The potential role of these transmitters is discussed later.

The above discussion confirms that the antinociceptive action of epibatidine is mediated by activation of nAChR. However, nicotinic agonists have a multitude of effects through interaction with central and peripheral (ganglionic and neuromuscular junction) nAChR. Unfortunately, from a drug therapeutic viewpoint, epibatidine shows a full spectrum of nicotinic effects, with changes seen in animal activity, body temperature and cardiovascular and respiratory systems at doses comparable with those affording antinociception. For example, in the hotplate test, significant antinociception in mice is associated with the same dose range of epibatidine as temperature and locomotor effects,[10,27,40,65] which are also thought to involve central nAChR.[40,45] This wide spectrum of actions attributable to epibatidine is a problem from two viewpoints. First, it makes the compound unacceptable as an analgesic agent for clinical use and second, as measures of antinociception invariably involve a behavioural end-point (that is, withdrawal of tail or foot) in response to a heat stimulus, then effects on several nicotinic systems could cause problems in interpretation of data from animal experiments. In particular, if motor activity is decreased then an increased latency to the behavioural response after the nociceptive stimulus will be seen and interpreted as an "analgesic" response. Motor defects could be contributing to, or even responsible for, the observed antinociception. Consequently, there is doubt as to whether real analgesia would be seen with these compounds in man.

It is therefore important to be able to separate any real antinociceptive action of epibatidine from motor and temperature effects in animal experimental models. Although effects on rodent activity are seen at antinociceptive doses it has been suggested that motor impairment may not be evident at these levels and therefore may not interfere with the behavioural measures.[63] In support of this, the reduction in motor performance has a slightly different time course from antinociception, which may indicate that locomotor changes are not entirely responsible for the antinociceptive response.[10] Furthermore, the antagonist mecamylamine blocks the effects of epibatidine on activity, temperature and antinociception when given before the epibatidine but when given after epibatidine blocks only the latter two effects and may enhance the nociceptive response.[10] This indicates a separation of antinociception from other, interfering, nicotinic effects of epibatidine, and perhaps a role for different nAChR in the various responses. Indeed, there are several lines of pharmacological evidence for differential receptor interactions at central nAChR. Some nicotinic agonists have antinociceptive properties in the mouse, whereas others have not been reported to show such activity.[23] In rats i.t. epibatidine affords a nociceptive response, which may be caused by the release of excitatory amino acids, at lower doses than its antinociceptive effect.[40] Unlike nicotine, epibatidine shows no evidence of anxiolytic activity, which again indicates different nAChR, although it is possible that toxic effects mask any anxiolytic activity.[65] However, the best pharmacological evidence for the activation of different subtypes of nAChR would come from studies with antagonists. There are two types of blockers of central nAChR: competitive, which act at the acetylcholine binding site and may be typified by dihydro-β-erythroidine; and non-competitive channel blockers such as mecamylamine. Mecamylamine has no selectivity but dihydro-β-erythroidine has some differential activity across central nAChR.[2,33] Both antagonists reduced the effect of epibatidine in the mouse hotplate test, though dihydro-β-erythroidine may be less effective[6,58] and does not appear to inhibit the antinociceptive response to i.t. epibatidine.[40]

All these differences support the concept that action at heterogeneous nicotinic receptor types within the central nervous system, either in terms of receptor recognition or efficacy of the different ligands, may mediate different actions and that targeting specific receptor types may provide leads to develop selective agents.

Epibatidine and nicotinic receptors

NICOTINIC RECEPTORS

Biochemical and molecular studies of nAChR indicate a high potential for subtype diversity within this class of receptors. Nicotinic receptors for acetylcholine are members of the ligand-gated ion channel superfamily. The nAChR is a protein complex composed of five peptide subunits that provide a ligand binding site and which make up an ion channel that allows the passage of Na^+ and Ca^{2+} ions, after agonist binding. Each of the five subunits is comprised of an extracellular, relatively hydrophilic *N*-terminal domain where acetylcholine binds, three hydrophobic transmembrane domains, a larger intracellular loop and a fourth hydrophobic transmembrane domain.[47] Four different types of peptide subunit can make up the channel, namely α, β, γ and δ. The neuromuscular junction nAChR is composed of α, β, γ and δ subunits and is termed the α1β1γδ receptor. However, δ and γ subunits are not found in the central nervous system, where only α and β subunits have been described, although these have a somewhat different amino acid composition from the α and β subunits that are part of the neuromuscular junction receptor. Indeed, in brain tissue from several species, including human, genes coding for 11 different subunits have been described.[41,47] These 11 genes code for eight α-subunits (α2–9) and three β-subunits (β2–4). Consequently receptors could exhibit a great deal of molecular diversity, whether composed of a selection of these α and β subunits or even of α-subunits alone. The subunits that make up the receptor govern its functional properties and pharmacological properties. The binding site for acetylcholine is on an α-subunit, but it is the particular combination of subunits, and consequently of amino acid residues lining the channel, that controls the properties of the channel and of the receptor, such as ligand specificity, ion selectivity, open times and rate of desensitization.

In spite of the extensive molecular diversity theroetically made possible by combination of the eight α-subunits and three β-subunits, only three different recognition sites have been described in brain homogenates using ligand-binding techniques.[44, 61] These are sites with high affinity for (–)$[^3H]$nicotine (affinity 0.5–5 nM), sites with high affinity (0.5 nM) for α-bungarotoxin and sites with high affinity for neuronal bungarotoxin. At these latter two sites (–)-nicotine has affinity at the μM level. $[^3H]$epibatidine binding to homogenates of brain[35] and spinal cord[40] shows further heterogeneity with high-affinity (40–70 pM) and low-affinity (230–360 pM) sites. Neither of these sites appears to be the α-bungarotoxin binding sites. The high-affinity binding sites for $[^3H]$nicotine show a relationship with the distribution in brain of an nAChR consisting of the α4β2 subunit combination. In fact 90% of high affinity $[^3H]$nicotinic binding sites in rat brain can be precipitated by antibodies raised against α4 and β2 subunit peptides, suggesting that this is the predominant nAChR receptor in brain.[29, 75] Similar studies indicate that the receptors defined as α-bungarotoxin binding sites may be composed only of α-7 subunits. These sites appear to be highly permeable to Ca^{2+} ions; they quickly activate and inactivate and may play an important role in synaptic transmission.[3] Another subunit combination that is of special relevance to studies of epibatidine is the α3-containing receptor combined with either β2 or β4, which is thought to be the ganglionic-type nicotinic receptor.[43]

As in many fields of neuroscience, the study of nAChR has benefited enormously from the ability to express individual receptor subunits in *in vitro* cell systems and in different combinations. Ligand binding to specified subunit combinations can then be studied in isolation, and the efficacy with which different ligands activate these different subunit combinations to alter cellular events can be measured. From these studies it has been shown that the number of possible receptors is restricted, because not all are able to make functional receptors. In fact just 11 different functional receptors have been identified by co-expression methods using cDNAs for different subunits. There are several recent comprehensive reviews on different nAChR.[13, 17, 41]

Epibatidine actions at nicotinic receptors

At central nAChR, epibatidine has much higher affinity than acetylcholine or nicotine (table 1). At the predominant α4β2 receptor[32, 66] (+)- and (–)-epibatidine have very high affinity, around 20 times greater than that of (–)-nicotine. In addition, epibatidine is a potent agonist at the α4β2 receptor, being some 200 times more potent than (–)-nicotine, and also more efficacious[32] (table 2). Like nicotine, epibatidine has less affinity for the α7 receptor (300-fold less than its affinity for the α4β2 subtype), but this is still 100 times better than the affinity of nicotine for this receptor (table 1) and epibatidine is about 40 times more potent than nicotine as an agonist at this receptor[32] (table 2).

Epibatidine differs from acetylcholine and nicotine in possessing high affinity for peripheral nicotinic receptors, the α1β1δγ neuromuscular receptor and the α3 subunit containing receptors that constitute the ganglionic-type receptors (table 1). At both of these nAChR types, epibatidine is a potent agonist (table 2). At the ganglionic-type nAChR endogenously expressed in the human neuroblastoma cell line IMR-32,[43] epibatidine is >1000-fold more potent than (–)-nicotine and at α3β4 receptor injected into oocytes, epibatidine is approximately 1000 times more potent than nicotine or acetylcholine with an EC_{50} of around 20–130 nM.[31] These *in vitro* data agree with findings that show that epibatidine behaves as a potent agonist in isolated preparations of rat and guinea-pig autonomic ganglia[11] and is a potent ganglionic agonist *in vivo*, leading to nicotinic-like cardiovascular effects and respiratory stimulation in the anaesthetized rat that are reversed by the ganglion-blocker trimethaphan.[27] At high doses the compound produces a depolarizing blockade. In contrast, no effect was observed on neuromuscular transmission, suggesting the compound has higher potency at ganglionic as compared with neuromuscular nicotinic receptors. This agrees with findings *in vitro*, where the potency of epibatidine is at least 10 times higher at receptors containing α3 subunits than at those containing α1 (neuromuscular-type) subunits[31] (table 2). Even so, epibatidine has high affinity in the low nM range for the neuromuscular receptor type and has the highest affinity of all nicotinic agonists at the α1β1δγ neuromuscular receptor.

One perhaps surprising difference between nicotine and epibatidine is in the stereochemistry of the interaction with neuronal nAChR. In addition to labelling more sites in central nervous tissue, epibatidine binds and acts at the nAChR in a non-stereoselective fashion. The (–)- and (+)-isomers have similar affinity and similar potency in pharmacological assays and as antinociceptive agents.[6, 20, 58] In contrast (–)-nicotine binds 20 times more effectively to nAChR than the (+)-isomer. However, this appears

Table 1 Affinity (*Ki*) of epibatidine isomers for different nicotinic acetylcholine receptors (nAChR) *in vitro*

	Ki (nM)			
	α4β2	α7	α3β2/4	α1β1δγ
(–)-Epibatidine	0.06	16	0.15	5.7
(+)-Epibatidine	0.05	22	0.23	2.5
(–)-Nicotine	1.0	2000	5	10 000

All receptors are human clones except torpedo α1β1δγ. Data from reference 66 except α3β2/4 data, which are from references 31 and 43. Values are from receptors in different expression systems, so comparisons can be only approximate.

Table 2 Agonist potency of epibatidine at different nicotinic acetylcholine receptors (nAChR) *in vitro*

	EC_{50} (nM)			
	α4β2	α7	α3β4	α1β1δγ
(±)-epibatidine	17	1100	19	1600*
(–)-nicotine	4000 (PA)	40 000	14 000	250 000

Data are from references 32, 55 and 31, and are for human receptors except α1β1δγ (torpedo). Values are from receptors in different expression systems and using different measures and so should be compared approximately. PA = partial agonist. *Data for (+)-epibatidine.

to be a property specific to *N*-methyl substituted compounds, like nicotine, because (–)- and (+)-nornicotine are not differentiated in binding to nAChR.[77]

Visualization of central nicotinic receptors with epibatidine

While nicotine and related compounds label only subsets of nicotinic receptors, epibatidine labels a much wider range of nAChR. This ability of $[^3H]$epibatidine to label nicotinic receptors has been used to map nicotinic receptor sites in brain.[53] The distribution of nicotinic binding sites in the central nervous system, labelled by $[^3H]$nicotine, shows sites in layers III and IV of the cerebral cortex, the thalamus, interpeduncular nucleus and superior colliculus, with lower levels in the hippocampus and hypothalamus and layers I and IV of the cerebral cortex.[16] This probably reflects the distribution of the predominant $\alpha 4\beta 2$ receptor. The binding of $[^3H]$epibatidine closely follows this pattern but in addition $[^3H]$epibatidine labels areas in the visual system (optic nerve, optic chiasm, optic tract, pretectal nuclei, superficial grey of the superior colliculus), and areas that are thought to be involved in the integration of olfactory and sensory signals (medial habenula, fasciculus retroflexus). It is possible that this represents binding to receptors containing the $\alpha 3$ subunit.[53] In fact $[^{125}I]$epibatidine labels nicotinic receptors in superior cervical ganglia that do not express mRNA coding for $\alpha 2$ or $\alpha 4$ subtypes and are likely to contain the $\alpha 3$ subunit. The distribution of sites labelled by neuronal bungarotoxin and α-bungarotoxin are very different, suggesting these are not labelled by $[^3H]$epibatidine.

Derivatives of epibatidine such as $[^{125}I]$IPH[22, 52] and $[^{18}F]$FPH,[34] in which the Cl substituent is replaced by $[^{125}I]$ or $[^{18}F]$ respectively, match the distribution of $[^3H]$epibatidine. These and $[^{11}C]$-*N*-methylepibatidine[73] may be useful for *in vivo* imaging of brain nicotinic receptors. $[^3H]$epibatidine itself has been used to show selective losses of receptors in brains from patients with Alzheimer's disease, suggesting that the $\alpha 4\beta 2$ subtype might be the most vulnerable in this disease.[71]

Mechanism of antinociceptive action of epibatidine

NEUROTRANSMITTER RELEASE

Evidence has been provided to show that epibatidine acts as an antinociceptive agent through central nAChR, and that such receptors also mediate many other actions of nicotinic agonists. As discussed above, the antinociceptive properties may not be real because behavioural end-points are used in the animal tests. Nevertheless, it is important to understand what effects different central nAChR mediate, and how this could explain the observed antinociceptive response. In particular, activation of nicotinic receptors has been shown to cause the release of neurotransmitters. Epibatidine and other nicotinic agonists have been reported to release catecholamines by a Ca^{2+} dependent mechanism,[4, 59] excitatory amino acids[40] and 5-HT.[74] As pathways involving these transmitters have been implicated in nociceptive processing,[26] such effects may contribute to the antinociceptive actions of nicotinic agents.

Epibatidine produces a concentration-dependent increase in $[^3H]$dopamine release from rat striatal slices and $[^3H]$norepinephrine release from slices of hippocampus and thalamus.[59] The release profile is similar to that of (–)-nicotine with similar maximal effects, although epibatidine is 50–4000 times more potent, depending on the response measured. This difference is caused by the differential activity of nicotine across the different measures, because epibatidine is equally potent for each effect. The release of neurotransmitters in these experiments was blocked by mecamylamine and the release of norepinephrine, but not dopamine, was blocked by tubocurare. A similar profile is seen with nicotine-evoked release of norepinephrine.[76] Dihydro-β-erythroidine has the opposite profile. These antagonist studies indicate that different nAChR subtypes may be involved.

A role for adrenergic systems in the antinociceptive action of epibatidine has to be confirmed. However, antinociceptive responses to epibatidine and nicotine in the tail-flick test are significantly attenuated by pretreatment with phenoxybenzamine to remove adrenergic receptors and by *N*-(2-Chloroethyl)-*N*-ethyl-2-bromobenzylamine (DSP-4), a neurotoxic agent leading to a reduction in norepinephrine concentrations, some reduction in 5-HT concentrations but no reductions in dopamine concentrations.[57] This implicates noradrenergic systems in the antinociceptive actions of epibatidine and nicotine. In a similar tail-flick procedure yohimbine, a non-selective adrenergic antagonist, is reported not to block epibatidine-induced antinociception in mice or rats,[56] although others have shown an inhibition of nicotine-induced antinociception by yohimbine.[15, 67] Thus the actual role of adrenergic receptors remains unclear.

The pharmacology of dopamine release from striatal slices suggests a role for nAChR different from norepinephrine release. However dopamine is unlikely to be involved in the antinociceptive response to epibatidine because nicotine-induced antinociception is not blocked by the dopamine DA1-receptor antagonist SCH23390 or the DA2-receptor antagonist sulpiride.[19] Rather, dopamine is important in other aspects of epibatidine's nicotinic pharmacology. *In vivo* epibatidine induces turning behaviour and an increase in locomotor activity, at least in some models, which are blocked by D1 and D2 antagonists.[59] The time course of these responses is relatively slow, occurring 15 min after injection and lasting for 60 min. Moreover, the doses of epibatidine needed are large compared with those that give an antinociceptive response. In addition, animals trained to discriminate nicotine recognize epibatidine as a full agonist 190 times more potent than nicotine itself. This nicotine cue probably involves dopamine release.

Opioids are well known to mediate their effects partly by inhibiting the release of nociceptive neurotransmitters, in particular substance P [see reference 62 for review] from primary sensory afferent neurons in the dorsal horn of the spinal cord. Nicotinic receptors are well represented in this area[39, 78] and it is conceivable that a similar mechanism could exist for these compounds. However, in peptidergic cells expressing ganglionic-type receptors, epibatidine enhances the release of substance P in a mecamylamine-sensitive manner.[55] This could be the mechanism behind the pain response seen after i.t. epibatidine,[40] and may conceivably be responsible for the antinociceptive action by depleting stores of nociceptive neurotransmitters. In addition, these receptors desensitize very rapidly and thus desensitization of neurons to noxious stimuli may be a potential antinociceptive mechanism.

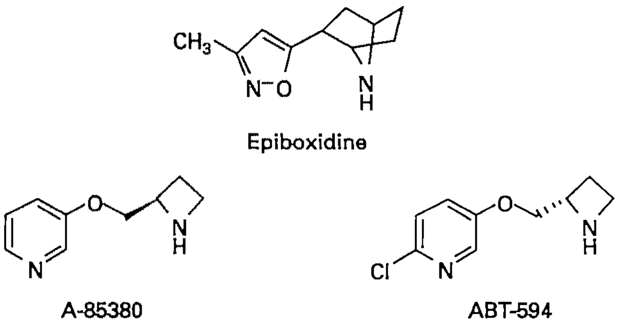
ROLE OF CALCIUM

Although the role of Ca^{2+}-dependent neurotransmitter release in the antinociceptive action of epibatidine is not proven, there is direct evidence of a role for Ca^{2+} ions in the antinociceptive response to nicotinic agonists. Agents that raise intracellular calcium, namely the calcium channel agonist (±)BAY K 8644 (voltage-dependent channels), glyburide (ATP-gated K^{+} channels), thapsigargin (intracellular stores) and A23187 (extracellular stores), when given intrathecally, all significantly potentiate antinociception afforded by nicotine given s.c. in the mouse tail-flick test, without causing an antinociceptive action themselves at the doses and times used.[18] Nicotine antinociception is also blocked by nifedepine, again indicating involvement of L-type Ca^{2+} channels, although the interaction is probably indirect.[18] Similarly the Ca^{2+} channel activator (−)BAY K 8644 enhances epibatidine antinociception, and its isomer (+)BAY K 8644, an L-type Ca^{2+} channel blocker, inhibits the response.[8] The antinociceptive actions of epibatidine are not blocked by the α-bungarotoxin-sensitive antagonist methyllycaconitine, suggesting that these receptors are not involved in the antinociceptive action of epibatidine.[57] As discussed earlier, these are likely to be α7-type receptors that are highly permeable to Ca^{2+} ions. Neuronal nAChR are known to be highly permeable to Ca^{2+} ions, although less than α7-type receptors.[50 68 69] Moreover, external Ca^{2+} potentiates agonist action at neuronal nAChR by enhancing ionic current amplitudes and agonist affinity, probably by binding to an allosteric site on the receptor.[30 51] In addition to neurotransmitter release these Ca^{2+} fluxes may also be involved in longer-term plasticity changes.[50 69]

The future for epibatidine and nicotinic analgesics

Because of the undesirable pharmacological properties of opioids and public debate about their use, inadequate doses of these drugs are often prescribed and given.[64] There is no doubt that there is considerable interest in nicotinic agonists as analgesic agents that would present a clinical profile very different from that of the morphine-like analgesics. The wide diversity of nAChR suggests that the many nicotinic actions are mediated by different receptors. An understanding of these receptors and the roles they play should allow specific agonists and antagonists to be designed. For example, the isoxazole analogue of epibatidine, named epiboxidine (fig.3), has approximately 10-fold lower affinity than epibatidine for [^{3}H]nicotinic binding in rat cortical membranes.[7] In the hotplate assay the compound is about 10-fold less potent than epibatidine and at a maximal antinociceptive dose is considerably less lethal. In contrast, at the ganglion-type receptor in PC12 cells, epiboxidine has similar potency to epibatidine. Thus binding to central sites recognized by [^{3}H]nicotine, which represents the predominant α4β2 type, appears to be related to antinociception. Therefore one way to obtain an improved side-effect profile is to reduce the potency of epibatidine for receptors other than the α4β2 subtype. Considerable strides towards this aim have been made. Two compounds, A-85380[66] and ABT-594[9] (fig. 3) have the same affinity as epibatidine for the α4β2 subtype but have, respectively, >3000 or >100 000 lower affinity for the α7 and neuromuscular receptor subtypes. With A-85380, the functional activity seen at the ganglion-type receptor expressed in IMR cells is at a similar level to activity at the α4β2 receptor expressed in HEK cells,[66] although ABT-594 is reported to show reduced cardiovascular effects.[9] In rats, ABT-594 is approximately equi-efficacious with morphine in three different models of pain, in a mecamylamine-reversible manner. The compound is effective in a heat nociception assay, in blocking the second phase of the pain response after injection of formalin into the hind paw, a model for persistent pain, and in an allodynia model of neuropathic pain. Surprisingly, in view of the findings with epibatidine in peptidergic cells,[55] ABT-584 does inhibit capsaicin-induced release of substance P from spinal cord slices, and in dorsal horn neurons selectively inhibits activity in neurons activated by thermal and mechanical stimuli, but not by non-noxious stimuli. In addition the compound may activate descending pathways after injection into the brain stem.

Compounds like ABT-594 represent a major advance in the potential of nicotinic ligands to be developed as analgesic agents. It must be borne in mind that, although selectivity for central nAChR of the α4β2 type confirms that antinociception occurs *via* a centrally mediated mechanism, many of the other effects of nicotinic agonists are also centrally mediated. In addition, it is difficult to separate antinociceptive effects of nicotinic agonists from behavioural effects and antinociception with these compounds has been measured only in rodents. Therefore it is an open question whether analgesia without adverse nicotinic effects will be seen in humans with this class of drugs. In man, studies have suggested that tobacco smoking may invoke an analgesic effect,[25 54] although others show that smoking



Epiboxidine

A-85380

ABT-594

Figure 3 Epibatidine analogues.

has no analgesic effect[70] and may heighten sensitivity to pain.[48 49] ABT-594 will soon be undergoing safety trials in humans and may then undergo efficacy trials. The outcome of such studies with a highly efficacious (and, it is hoped, safe) nicotinic agonist will tell us whether such agents will be added to the armamentarium of the pain clinic. If they are, then the frog from Equador has done mankind a great service.

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Pharmacology and potential therapeutic uses of cannabis

R. A. Hirst, D. G. Lambert and W. G. Notcutt

Throughout history, cannabis has been used as a natural therapeutic herb. Indeed the discovery of the remains of a young girl in Jerusalem who died in childbirth sometime around the third century AD, revealed residues of cannabis in the pelvic region.[97] This strongly suggests that cannabis was used in medical practice in early human civilizations.

Cannabis was first used as a medicine in Britain in the mid-nineteenth century by O'Shaugnessy, an army surgeon. While in India O'Shaugnessy witnessed at first hand the use of cannabis for a wide range of medical conditions such as rabies, epilepsy and muscle spasms, and for pain relief. On his return to Britain, O'Shaugnessy advocated its use and cannabis was widely accepted as a medicine for about 70 years.[61 63]

In this article we shall review the pharmacology of cannabinoids and their therapeutic potential. In particular, we shall discuss their use as antinociceptive/analgesic agents. The reader is referred to several excellent review articles and books on this subject.[4 8 22 37 45 50 63 69 95]

The major psychoactive constituent of *Cannabis sativa* was first isolated in 1964.[32] The compound was identified as Δ^9-tetrahydrocannabinol (Δ^9-THC, fig. 1), and when administered to humans produced a spectrum of effects, including increased pulse rate, decreased blood pressure, muscle weakening, increased appetite, euphoria followed by drowsiness, depersonalization, altered time sense and decreased memory recollection; hearing became less discriminative and visual signals were sharper but distorted.[45] The effects of Δ^9-THC at the biochemical level were virtually unknown until recently. Pharmacological studies suggested that Δ^9-THC and other active cannabinoids might act at specific receptor sites,[38 68] but the high lipophilicity of these compounds made their use in binding assays very difficult. Some researchers were initially of the opinion that the effects observed with Δ^9-THC were attributable to perturbation of membrane structures.[45] However, these proposals were refuted and early attempts to identify specific cannabinoid receptor binding sites in brain membranes showed encouraging results.[64]

As early as 1984, Howlett and co-workers[47] showed that cannabinoids caused inhibition of adenylyl cyclase. It was subsequently shown that this effect was seen only in the presence of GTP and was sensitive to pertussis toxin pre-treatment, indicating a response mediated by G_i/G_o G-protein,[46 48] further indication of the presence of a cannabinoid receptor. The low potency and high lipophilicity of the cannabinoids led to the search for synthetic compounds with cannabamimetic activity.

Synthetic cannabinoid agonists

The discovery of cannabinoid receptors was undoubtedly facilitated by the synthesis of novel cannabinoid ligands, including levonantradol, nabilone, CP55,940 (6S-[3(R),6α,6aα,9α,10aβ]-(–)-5,6,6a,7,8,9,10,10a-octahydro-6-methyl-3-(1-methyl-4-phenylbutoxy)-1,9-phenanthridinediol 1-acetate hydrochloride), WIN55212-2 (R-(+)-(2,3-dihydro-5-methyl-3-[4-morponolinylmethyl]pyrol[1,2,3-de]-1,4-benzoxazin-6-yl(1-napthalenyl) methanone mono-methanesulphonate) (see fig. 1) and HU210.[27]

These compounds were generally slightly more hydrophilic and were more potent than Δ^9-THC.[18 49] In addition, the compounds had inactive stereoisomers that distinguished the non-specific effects of cannabinoids. Using the radio-labelled agonist $[^3H]$CP55,940, Devane and colleagues[18] demonstrated dose-dependent and saturable binding to brain membranes, an effect that was also dependent on GTP (see above).

These synthetic cannabinoid receptor agonists were tritiated and successfully used in radio-ligand binding assays to convince sceptics that cannabinoid receptors exist in both neuronal and peripheral tissues.[13 39 40 49 64] The discovery of specific cannabinoid binding sites was interpreted as evidence for a new putative cannabinoid receptor, and these reports were mainly responsible for the subsequent search for the cannabinoid receptor using molecular cloning studies.

CB1 and CB2 receptors

STRUCTURE AND FUNCTION

The neuronal cannabinoid receptor (CB1) was first cloned from the rat DNA library in 1990,[60] soon after

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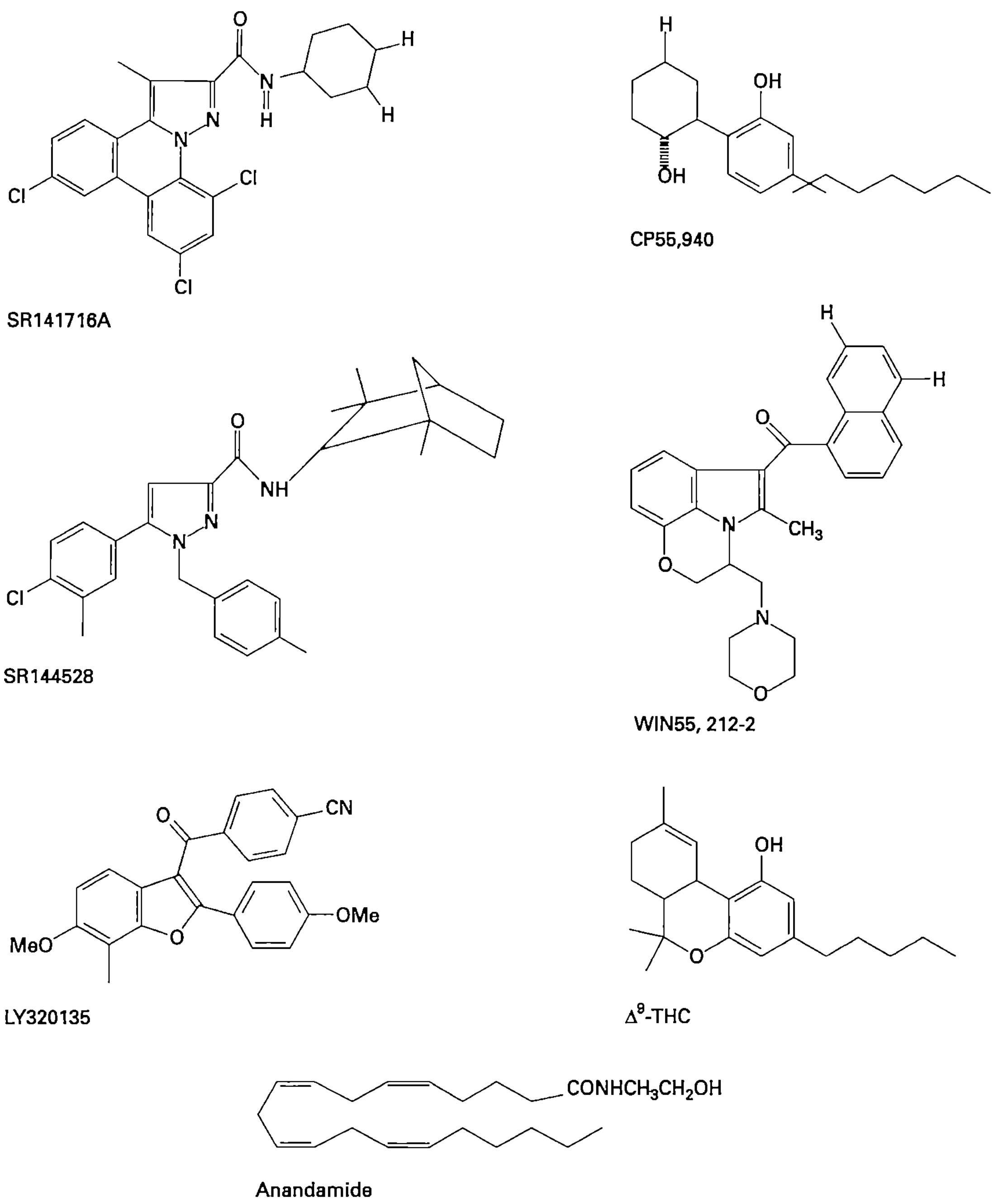

Figure 1 Structures of commonly used cannabinoid agonists and antagonists.

the human receptor was cloned.[33] Another isoform of the cannabinoid receptor was cloned from macrophages and spleen. This receptor showed only 44% homology with the CB1 receptor and was not expressed in the brain; it was termed the peripheral cannabinoid receptor or CB2.[62]

The cannabinoid receptor (table 1) belongs to the superfamily of G-protein-coupled receptors; it has seven transmembrane-spanning domains and an extracellular N- and an intracellular C-terminus, with several potential glycosylation sites. Translation of the CB1 cDNA resulted in a protein product consisting of 473 amino acids. The central cannabinoid receptor and the peripheral receptor have only approximately 44% overall homology, with 68% homology in the membrane-spanning regions.[62] Both the CB1 and CB2 receptors are coupled to a pertussis-toxin-sensitive G-protein that, when activated, results in agonist inhibition of adenylyl cyclase.[27,60]

The presence of a truncated isoform of the central cannabinoid receptor has been reported,[82] and termed CB1a. The pharmacology of CB1a is almost identical to that of CB1, except that agonist-binding affinity to CB1a is slightly reduced when compared with CB1.[78]

More recently, in an attempt to separate the euphoric effects of cannabinoids from their potential therapeutic effects, a series of propano-Δ^8-THC analogues have been synthesized.[72] These modified classical cannabinoids indicate that the carbon at position one in the molecule may be important in conveying CB2-receptor-selective activation, and they have generated a further CB2-selective research tool.

Table 1 Characteristics of cannabinoid receptors. VSCC=voltage sensitive Ca^{2+} channel; JWH-015=1-propyl-2-methyl-3-((1-napthoyl)indole), JWH-051=1-deoxy-11-OH-^{8}-THC-dimethylheptyl (see text for further information and structures); * modest selectivity; † inverse agonist activity also reported; ?=unclear

	Neuronal	*Non-neuronal*
Cloned and G-protein coupled	✓ CB1	✓ CB2
Location	CNS/periphery	Periphery
Inhibits adenylyl cyclase	✓	✓
Closes VSCC	✓	?✗
Enhances outward K^+ current	✓	?✗
Agonists (endogenous)	Anandamide	Palmitoyl-ethanolamide
Agonists (non selective)	Δ^{9}-THC CP 55940 WIN 55212-2 Nabilone	
Agonists (selective)	HU210*	JWH-015 JWH-051
Antagonists	SR141716A† LY320135	SR144528

RECEPTOR TISSUE DISTRIBUTION AND BASIC PHARMACOLOGY

CB1 receptors are present in the brain at very high concentrations; for example, Ney and colleagues[64] reported 1.2 pmol mg protein^{-1} in rat brain. Detailed autoradiographic studies have revealed the distribution of CB1 receptors in the brain. They are present in many brain regions, including olfactory areas, the cortex, hippocampus, cerebellum and basal ganglia, whereas the thalamus, hypothalamus and brainstem had few binding sites.[56] The few CB1 receptors present in the brain stem may explain the lack of respiratory depression observed with the use of cannabis. CB1 receptors are also found in the spinal cord.[35]

Using antibodies directed against the extracellular amino terminus of the CB1 receptor, Tsou and colleagues[92] have used immunohistochemical techniques to produce a more detailed picture of the distribution of the receptors in the central nervous system. The presence of CB1 immunoreactivity in some of the brain regions involved in nociception (periaquiductal grey, dorsal horn and lamina X) lends weight to the possibility that cannabinoids have antinociceptive actions.[59] In addition, some of the brain regions involved in GABAergic neurotransmission (hippocampal, cerebellar Purkinje neurons, striatonigral and striatopallidal neurons) were also rich in CB1 receptors where occupation increases GABAergic transmission.[34] Dopamine neurotransmission in the nucleus accumbens is stimulated by Δ^{9}-THC and heroin.[89] The effect on dopamine levels of both drugs was shown to be mediated by the μ_1 opioid receptor.[89] CB1 receptor mRNA has also been reported in a variety of peripheral tissues,[31] including lung[73] and intestine.[14 67]

CB2 receptors have been detected mainly in peripheral tissues, including spleen and macrophages.[62] There is now evidence that CB2 receptors are expressed in peripheral nerve terminals.[37 69] CB2 receptors are also found in the vas deferens and myenteric plexus, where electrically evoked contractions were inhibited in a dose-dependent manner by two newly available CB2 preferring agonists, JWH-015 (1-propyl-2-methyl-3-((1-napthoyl)indole)) and JWH-051 (1-deoxy-11-OH-Δ^{8}-THC-dimethylheptyl). These responses were not reversed by co-incubation with the cannabinoid CB1 antagonist SR141716A.[56]

BIOCHEMICAL PHARMACOLOGY

CB1 receptors are also naturally expressed in continuous cell lines, including NG108-15 where they cause inhibition of N-type VSCC,[9] and N18TG2 where inhibition of adenylyl cyclase has been reported.[47] They also couple to a blockade of long-term potentiation,[11] modulation of potassium-A currents,[16] inhibition of Na^+K^+- and $Mg^{2+}Ca^{2+}$-ATPase.[2]

Cloned CB1 receptors have been transfected into CHO (Chinese hamster ovary), Ltk (murine fibroblast) and AtT-20 (mouse pituitary) cells, none of which naturally express the receptor.[3 27 28] CP55,940 caused an inhibition of adenylyl cyclase in CB1-transfected cells only, whereas arachidonic acid release and intracellular Ca^{2+} release was observed in both CB1 transfected and untransfected cells; this report concluded that cannabinoids stimulate both receptor and non-receptor mediated signal transduction pathways.[28] In a later study, Felder and co-workers[27] compared the pharmacology of CB1 and CB2 receptors expressed in AtT-20 and CHO cells. They reported that both receptors bound cannabinoid agonists with varying affinity: CP55,940, anandamide and Δ^{9}-THC were equipotent at each receptor; WIN55212-2 and cannabinol bound with a higher affinity to CB2. Both receptors coupled to an inhibition of adenylyl cyclase in a pertussis toxin sensitive manner but only CB1 adenylyl cyclase inhibition was reversed by SR141716A. However in AtT-20 cells CB1 but not CB2 coupled to an inhibition of Q-type VSCC and a stimulation of the inwardly rectifying potassium channel. CB1 receptors have also been shown to activate mitogen-activated protein (MAP) kinases in CHO cells expressing CB1 receptors.[3]

Cannabinoid receptor antagonists

Studies on cannabinoid receptor pharmacology were hampered by the lack of availability of a specific antagonist. However, in 1994 Rinaldi-Carmona and colleagues[76] reported the synthesis and pharmacology of the first CB1-selective receptor antagonist, SR141716A (fig. 1).

In a later paper, it was shown that cannabinoid inhibition of cAMP formation was abolished by SR141716A and that oral administration of SR141716A in rats, abolished [^{3}H]CP55,940 binding to *ex-vivo* cerebellar membranes.[75] Using [^{3}H]SR141716A, which binds to the CB1 receptor independently of G-proteins, the same group reported the rank order binding affinity of cannabinoid ligands: SR141716A > CP55,940 > WIN55-212-2 = Δ^{9}-THC > anandamide.[79] The binding characteristics of [^{3}H]SR141716A have been confirmed (fig. 3).[44] Binding selectivity of SR141716A for CB1 over CB2 receptors in excess of 1000-fold has been reported.[26 27] Earlier this year the Sanofi group also reported the identification of the first CB2-selective antagonist, SR144528 (fig. 1). This compound showed some 700-fold selectivity for CB2 over CB1 receptors.[77] A second CB1-selective (~100-fold) antagonist, LY320135, has also been described.[26]

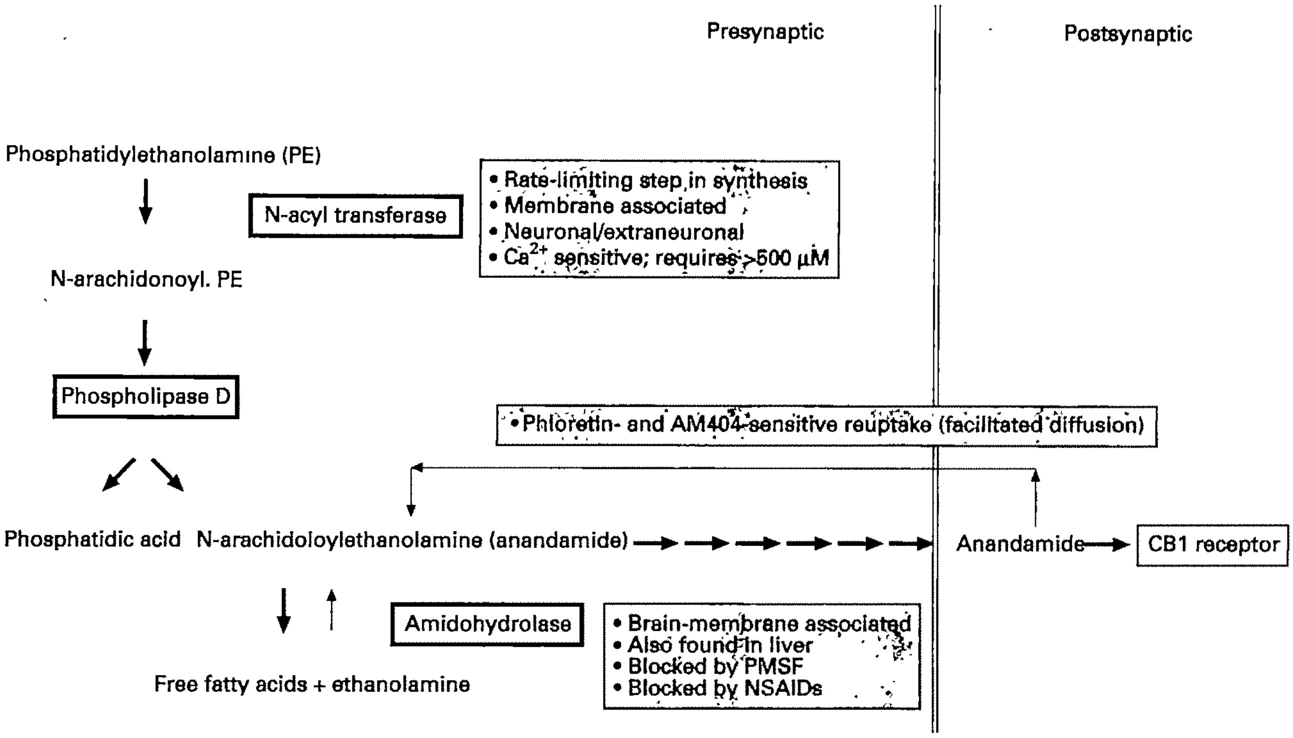
Presynaptic
Postsynaptic
Phosphatidylethanolamine (PE)
N-acyl transferase
• Rate-limiting step in synthesis
• Membrane associated
• Neuronal/extraneuronal
• Ca^{2+} sensitive; requires >500 μM
N-arachidonoyl. PE
Phospholipase D
• Phloretin- and AM404-sensitive reuptake (facilitated diffusion)
Phosphatidic acid
N-arachidoloylethanolamine (anandamide)
Anandamide
CB1 receptor
Amidohydrolase
• Brain-membrane associated
• Also found in liver
• Blocked by PMSF
• Blocked by NSAIDs
Free fatty acids + ethanolamine

Figure 2 Schematic representation of the synthesis/metabolism, release and reuptake of anandamide. PMSF; phenylmethylsolfonyl fluoride. NSAID; non steroidal anti inflammatory drugs.

Endogenous cannabinoid receptor ligands

Cloning of the cannabinoid receptor led to the hunt for the endogenous ligand(s). N-arachidonoylethanolamide or anandamide (fig. 1) was described by Devane and colleagues in 1992[17] as the endogenous agonist of the CB1 receptor. Since then the intricacies of the synthesis, degradation and pharmacology of this intriguing compound have emerged and have been the subject of an excellent review.[41] The rate-limiting enzyme in anandamide synthesis is N-acyl transferase. This enzyme is membrane associated and converts phosphatidylethanolamine to N-arachidonoyl phosphatidylethanolamine (N-APEA). The reaction is Ca^{2+} dependent but activated only at high concentrations.[19 20 21 41 87 88] The cleavage of N-APEA to produce anandamide and phosphatidic acid is catalysed by phospholipase D. Anandamide is not stored but is synthesized on demand.[19 20 21 41 87 88] In response to stimulation anandamide is released[23] and acts at the cannabinoid receptor to produce the cellular effects described above. Once released, anandamide is taken back up in a phloretin- and AM404 (N-(4-hydroxyphenyl) arachidonoylethanolamide)-sensitive manner.[7 41 42] Anandamide is broken down in CNS tissue by a membrane-associated amidohydrolase.[41] This enzyme is also found in the liver, is blocked by PMSF,[41] may be reversible[1] and is blocked by NSAIDs[29] (fig. 2). Anandamide is also metabolized by cyclooxygenase isoform 2[96].

Anandamide has been shown to displace radiolabelled cannabinoids from their receptor, inhibiting adenylyl cyclase in a pertussis toxin sensitive manner[94] and inhibiting N-type calcium currents.[35] Other groups have also shown that cannabinoid receptors can activate voltage-sensitive potassium channels in hippocampal cells[10] in a cAMP-dependent manner.[16] The CB1 receptor activation of K^+ currents has been hypothesized to play a role in decreasing presynaptic neurotransmitter release by restoring the resting potential of the neuron after action-potential-induced depolarization.[10] Anandamide displays modest selectivity for the CB1 receptor.[26]

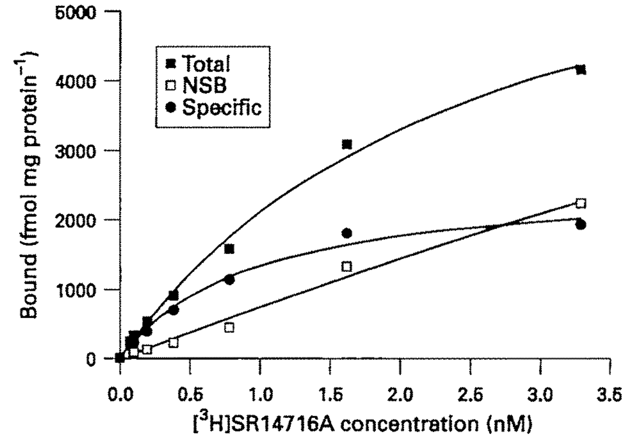

Figure 3 Dose-dependent and saturable specific binding of $[^3H]$SR141716A to the CB1 receptor in rat cerebellar membranes, revealing a B_{max} (maximum number of binding sites) of 2604 fmol mg protein^{-1} and a K_d (equilibrium dissociation constant) of 0.93 nM. Non specific binding (NSB) was determined in the presence of 1 μM unlabelled SR141716A, Specific binding is represented as the total minus the NSB. Figure redrawn from Hirst and colleagues.[44]

Several other endogenous ligands for the cannabinoid receptor have been described. Stella and colleagues[86] identified 2-arachidonylglycerol (2-AG) in intestinal tissue. However 2-AG is found at 170-fold higher levels in brain. Synthesis of 2-AG is also calcium dependent, under the control of phospholipase C and diglycerol lipase, and it acts as a full agonist at CB1 receptors, producing functional inhibition of long-term potentiation in the hippocampus.

Palmitoylethanolamide has been suggested as a putative endogenous agonist of the CB2 receptor.[24] This agent down-modulated mast cell activation, a response that is antagonized by anandamide. Further studies with this compound have demonstrated a Ca^{2+}-dependent synthesis[6] and a neuroprotective action in cultured cerebellar granule cells, an event mediated by a non-CB1 receptor.[83]

With details of the biosynthetic pathways for endogenous cannabinoids emerging, and details of the binding properties of these and other anandamide analogues[81] being reported, the clinical significance and therapeutic usefulness of these systems can be fully explored. It will be important to determine if anandamide/palmitoylethanolamide are involved in acute and chronic pain syndromes.

Therapeutic uses of cannabinoids

The schedule 1 status of cannabis has made modern clinical research almost impossible. This is primarily because of the legal, ethical and bureaucratic difficulties in conducting trials with patients.[4 22 95] Additionally, the general attitude towards cannabis, in which it is seen only as a drug of abuse and addiction, has not helped. There are numerous anecdotal reports of the benefits of cannabis in certain therapeutic situations (table 2).

Table 2 Potential therapeutic uses of cannabinoids

Antiemetic
Anticonvulsant
Muscle relaxant
Analgesic
Antiasthmatic
Immunosuppressant
Appetite stimulant
Insomnia
Glaucoma

The main therapeutic use of cannabinoids in man is as an antiemetic and there have been several clinical trials that have been reviewed extensively.[8 50 71] For example, Sallan reported that 10 mg THC m^2 body area produced a significant antiemetic effect in most of the 22 patients studied. However somnolence was a particularly troublesome side effect.[80] Paradoxically, this side effect may be of benefit in the treatment of insomnia. Nabilone is currently used as an antiemetic in cancer chemotherapy and has been used as a potential analgesic (see below). Cannabinoids reduce intraocular pressure and this action is useful in the treatment of glaucoma. The clinical data come from case reports[37] and the authors are unaware of any clinical trials of the effectiveness of this treatment. For the treatment of epilepsy and movement disorders (multiple sclerosis, Parkinson's disease, Huntington's disease) the evidence is again anecdotal and case-report orientated.[37] One controlled study reported an increased seizure-free period when cannabidiol was added to routine antispasmodic therapy.[15] This study is interesting in that the cannabinoid chosen, cannabidiol, is relatively weak in laboratory studies (see, for example, reference 60). Smoked cannabis has bronchodilatory activity that may be useful in the treatment of asthma.[90] However, this possible benefit must be set against the longer-term effects of tobacco inhalation. In 1991 Plasse and colleagues[70] reported that dronabinol (Δ^9-THC) was an effective appetite stimulant in a group of 10 patients with AIDS. These data agree with the well reported "munchies" experienced by recreational cannabis users.

Antinociceptive effects of cannabinoids and their use for the relief of pain

ANIMAL STUDIES

The major active constituent of cannabis Δ^9-THC has been shown to possess antinociceptive activity.[5 57 91] Its potency compared with morphine seems to depend on the route of administration.[58] The observation that SR141716A (a CB1 antagonist) reversed these effects definitively confirmed that the antinociceptive effect of Δ^9-THC is mediated by CB1 receptors.[12 76] Moreover, studies with SR141716A have revealed tonic cannabinoid antinociceptive activity, in that administration of the antagonist alone to mice produced a hyperalgesic response.[74] The antinociceptive activity of cannabinoids is not limited to Δ^9-THC as WIN 55,212 and CP 55,940 also display activity in rodent tail-flick tests.[25 54] In addition, anandamide administered i.p., i.v. or i.t. produced antinociception in mice.[30 84] In a study by Lichtman[53] the posterior ventrolateral periaqueductal grey was identified as an important area involved in CP 55,940 antinociception in rats.

Cannabinoid receptors are located in the spinal cord[92] and i.t. administration of cannabinoid agonists may have the potential to produce antinociceptive effects without the commonly observed psychotropic effects. In rodents i.t. cannabinoids exert antinociceptive effects[51 85] and this may involve activation of descending inhibitory processing.[52] Tsou and colleagues[93] demonstrated that systemic administration of WIN 55,212 suppressed formalin-induced c-fos expression in the rat spinal cord, indicating that cannabinoids also inhibit spinal processing of noxious stimuli.

In summary, cannabinoids are likely to produce antinociceptive actions in rodents at both spinal and supraspinal sites.

HUMAN STUDIES

As a result of the restricted availability of cannabinoids, controlled clinical trials of analgesic activity are rare. To our knowledge only one controlled trial has been reported[66]; in this study, THC 20 mg was comparable with codeine 60 or 120 mg in cancer pain. Grinspoon and Bakalar[37] commented on case histories describing the use of cannabis for analgesia in disorders including migraine, neuralgia and dysmenorrhoea.

Nabilone has been available for about 20 years for the management of intractable nausea and vomiting after chemotherapy for malignancy. Unfortunately, its side effects of drowsiness and dysphoria made it a drug of last resort, to be tried only when conventional antiemetics such as metoclopramide had failed. Eclipsed by the arrival of ondansetron and its analogues, nabilone is now rarely used for this purpose but remains available for medical use. The knowledge that cannabis might be successful in the relief of pain, coupled with the availability of nabilone, has led some to explore the use of nabilone for patients in intractable pain. No formal clinical trials of nabilone in chronic pain have been undertaken, and all information has been gathered from clinical observation of individual patients who have used the drug.

Nabilone is produced as a 1 mg capsule but a 10-fold dosage range has been used by one of the authors (WN), starting with 0.25 mg (obtained by opening the capsule and dividing the resultant powder accordingly). Most patients tolerate nabilone better at night, as sleep can ameliorate the side effects. Once the patient's confidence has been developed, the dosage has been increased where appropriate and where tolerable. Some of the indications for nabilone are listed in table 3.

For the control of neurogenic pain the success rate with nabilone may be no more than 30%, and a significant number of patients abandon the drug because of dysphoria and drowsiness. The range of benefits that have been observed during attempts to treat more than 50[65] patients includes analgesia, pain distancing, compressing the pain, sleep, relief of muscle spasm, relief of bladder spasms, relief of constipation, relaxation, anxiolysis, relief of depression and euphoria.

All patients who have tried cannabis as well as nabilone have preferred the former, because of overall effectiveness, less dysphoria and ease of titration (when smoking). This may reflect differences in both chemistry and route of administration.

Table 3 Use of nabilone in pain of various diagnoses

Neurogenic pain
Multiple sclerosis
Phantom limb
Diabetic neuropathy
Spinal cord injury
Nociceptive pain
Chronic back pain
Spinal sprains
Malignancy
Idiopathic Pain

Summary and future prospects

A detailed picture of the physiology and pharmacology of cannabinoids is emerging. Both a central and peripheral receptor have been cloned and putative endogenous agonists identified. The pharmaceutical industry has provided researchers with a wide range of tools to probe the cannabinoid system, and antagonists for both forms of the receptor are available. Statements from recreational cannabis users, together with case reports, anecdotal evidence, a few limited clinical trials and animal work, suggest great therapeutic potential for cannabinoids.

Clinical research into cannabinoids is in its infancy, and existing information provides no more than indicators for future studies. Nabilone is unlikely to be the most suitable drug and it may be that combinations of natural cannabinoids and assessment of different routes of administration offer the best chance of achieving therapeutic effects. With the distribution of human cannabinoid receptors reasonably well known and their expression in the spinal cord,[35] perhaps it is time to be bold and consider extradural administration.

Many patients are already illegally using cannabis to control the symptoms of their disease (for example, multiple sclerosis and cancer). Their needs must be addressed while formal studies are undertaken, and this will be an even greater challenge to resolve effectively.

While patients with intractable pain are an obvious target, other groups of patients may benefit in situations where strong analgesics are already used (for example, adjuvants in cancer, muscle spasm with acute injury, sedation in intensive care, premedication, etc.). There is a wide range of possibilities and a massive opportunity for research, if the legal and bureaucratic problems can be resolved. However, until adequate simple trials can be conducted, the therapeutic exploitation of cannabinoids will remain no more than a promising idea.

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CITATION CLASSIC

Commentary

Gustafsson LL, Schildt B, Jacobsen K. Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. *British Journal of Anaesthesia* 1982; **54**: 479–486.

In looking again at this paper, my thoughts are much the same as they were when it was originally published. A retrospective survey, even one with a high response rate, is a far from ideal way of assessing a problem, but the paper clearly demonstrates two points.

The first is that the rate of uptake of the use of "spinal" opioids (see fig. 1 of the original article) is clear evidence of the widespread recognition that a "peripheral" method of producing profound analgesia without adverse effects is highly desirable. The second point is, of course, that respiratory depression is a significant problem with this method of pain relief. My new, and disappointed, reaction is that although the lack of controlled clinical studies was recognized in 1982 it had not really been addressed when the subject was reviewed in this journal 7 years later,[1] and that we are not yet a great deal further forward.

Retrospective surveys have a reputation for drawing positive responses, but the incidence of respiratory depression after extradural morphine in this paper (< 0.5%) is much lower than in many subsequent reviews.[1] Many of the Swedish patients were receiving opioids for chronic pain and this might explain the low incidence, but most workers now prefer to use the more lipid-soluble opioids because of a perceived, if not proven, lower risk of respiratory depression. There remain many questions that require a definitive answer, such as which drug, what dose, and what level of supervision? The problem is that the answers will be provided only by studies enrolling large numbers of patients, which are not easy to mount.

It is widely accepted that the administration of one drug by one route for severe pain will either be less than fully effective or lead to complications, no matter what the technique or drug. This article was part of the evidence that convinced me that spinal opioids, used on their own, do not have an acceptable therapeutic ratio. My current practice is based on the view that local anaesthetics and opioids are synergistic when used spinally. If I am using a spinal anaesthetic and expect the patient to experience severe pain when the local anaesthetic regresses, I add a small dose of opioid to ease the transition to systemic analgesia.[2] For postoperative extradural infusions, I add some opioid to a dilute solution of local anaesthetic.[3] In both instances, my preference is for diamorphine, but it is not universally available and there is little objective evidence on drug suitability.

As for monitoring, I take the view that one should not, without very good reason, use an analgesic technique that requires a greater degree of supervision than the patient would receive for the associated surgical procedure. The charting of respiratory rate may not be considered a significant safeguard, but it does draw the attention of the nurses to the potential problems and increases the level of supervision. Finally, if a patient who has received spinal opioids suffers severe pain, an anaesthetist should be called before additional opioids are given.

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ADVERSE EFFECTS OF EXTRADURAL AND INTRATHECAL OPIATES: REPORT OF A NATIONWIDE SURVEY IN SWEDEN

L. L. GUSTAFSSON, B. SCHILDT AND K. JACOBSEN

SUMMARY

The Swedish Society of Anaesthetists conducted a nationwide retrospective survey of clinical experience with extradural and intrathecal opiates. Special interest was focused on the frequency and type of ventilatory depression. The questionnaire was answered by 84 of 93 departments (90%). Up to May 1981 extradural morphine had been given to approximately 6000–9150 patients, extradural pethidine to 220–450 and intrathecal morphine to 90–150 patients. Ventilatory depression requiring treatment with naloxone was reported in 23 patients treated with extradural morphine (0.25–0.40%) and in six given intrathecal morphine (4–7%). In 22 patients the administration of extradural morphine was considered as a major contributory factor for the occurrence of ventilatory depression. Only two of these 22 patients experienced ventilatory depression later than 6 h after the last dose of opiates (s.c., i.m., i.v. or extradural). Patients aged 70 yr or more, those receiving thoracic extradural puncture and those with reduced ventilatory capacity seemed to be overrepresented.

In 1979 it was demonstrated that small doses of morphine given intrathecally and extradurally produced long-lasting relief of chronic and postoperative pain in man (Bahar et al., 1979; Wang, Nauss and Thomas, 1979). The practice of this promising technique to achieve selective spinal analgesia has been hampered by the lack of controlled clinical studies (Editorial, 1980) and by reports of adverse reactions (Editorial, 1980; Reiz and Westberg, 1980; Yaksh, 1981). Pruritus and urinary retention are frequent side-effects (Reiz and Westberg, 1980; Samii, Chauvin and Viars, 1981).

An alarmingly high frequency of late respiratory depression after intrathecal administration (Davies, Tolhurst-Cleaver and James, 1980; Gjessing and Tomlin, 1981) and occasionally after extradural morphine (Boas, 1980; Christensen, 1980; Reiz and Westberg, 1980; Gustafsson, Feychting and Klingstedt, 1981) has been published.

The Swedish Society of Anaesthetists contacted the departments of anaesthesia in Sweden about the use and safety of extradural and intrathecal opiates for pain relief in clinical practice. The other aim was to estimate the frequency and elucidate the presentation of ventilatory depression after administration of extradural opiates to help in identifying patients with an increased risk for this side-effect.

MATERIALS AND METHODS

A questionnaire was sent to the head physicians of the 93 departments of anaesthesia in Sweden requesting them to report if they had used extradural or intrathecal opiates up to April 30, 1981. If so, they were asked about:

Use of extradural opiates

(a) Year and month when the department used extradural opiates for the first time.
(b) If the method was still in use, they were requested to report the indications for intra- and postoperative treatment of pain and for treatment of pain in obstetric, cancer or trauma patients.
(c) Type and amount of opiates and solutions administered extradurally.
(d) The number of patients treated with extradural morphine, pethidine or any other opiates up to April 30, 1981. If exact figures could not be given, approximate data were requested: 1–10, 11–25, 26–50, 51–100, 101–200, 201–500, 501–1000 or more than 1000 patients.

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Adverse reactions to extradural morphine

We asked about the number of patients who had experienced ventilatory depression requiring naloxone, severe pruritus, neurological sequelae, urinary retention or other adverse reactions.

The reported cases of ventilatory depression were followed up by direct contact with the reporting physicians. Special interest was focused on type of operation and anaesthesia and amount of opiates administered during the periods before, during and after operation. Such data and the use of other drugs, were recorded from anaesthetic and postoperative charts.

The patients were classified into three groups: patients given extradural morphine (i) within 1 h after anaesthesia, (ii) 1 h or later after anaesthesia and (iii) patients with cancer or trauma.

Use of intrathecal opiates

Information of the same type as was requested under the previous two headings was asked for. However, the reported cases of ventilatory depression were not followed up by direct contact with the reporting physicians.

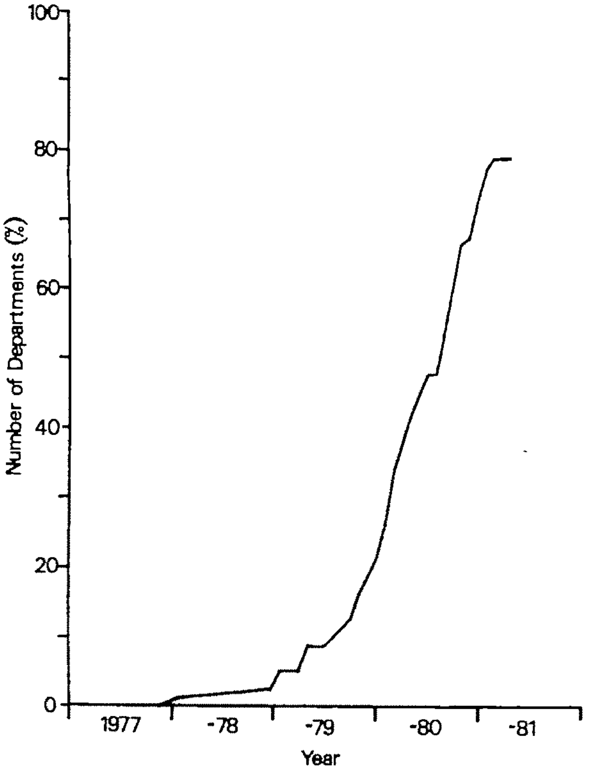

FIG. 1. The cumulative number of departments of anaesthesia in Sweden ($n = 84$) where extradural opiates were administered from 1977 to May 1981.

RESULTS

The requested information was obtained from 84 of the 93 departments (90%). Extradural opiates had been used in 67 departments and intrathecal in 10.

Use of extradural opiates

The percentage of the 84 departments that had used extradural opiates increased from less than 10% in June 1979 to more than 70% at the end of 1980 (fig. 1). This technique was still in use in 64 of 67 departments.

Between 6000 and 9150 patients were treated with extradural morphine, 220–450 with pethidine and none with other opiates. The stated standard dose of morphine for postoperative patients receiving the drug via a lumbar catheter was 2 mg in 17 departments and 4 mg in 37. At the thoracic level 2 mg was used in 17 and 4 mg in 14 hospitals.

Indications for using extradural opiates were received from 63 departments. Postoperative pain was widely accepted (83%), followed by trauma (64%), cancer pain (52%), intra- and postoperative pain (35%) and pain of obstetric procedures (6%).

Adverse reactions to extradural morphine

In 37 of the 67 departments where extradural morphine was used adverse reactions had been observed.

Ventilatory depression. Twenty-three instances of ventilatory depression requiring naloxone were reported from 15 departments. The administration of extradural morphine was considered as a major or contributory reason for the depression in 22 (tables I–III, unlikely for patient No. 23).

Only three of the 22 patients did not receive opiates additional to extradural morphine in the periods during or after operation (patients Nos 12, 14, 16). Ten of them were aged 70 yr or more and 10 had thoracic injections.

The majority of the cases of ventilatory depression occurred soon after administration of extradural morphine (fig. 2). Seven of 22 patients had depression later than 6 h after the last extradural dose of morphine. Depression more than 6 h after the last dose of opiate (as i.v., i.m., s.c. or extradural) was seen in only two patients (fig. 2).

TABLE I. *Patients with ventilatory depression (extradural morphine given within 1 h after anaesthesia)* (n = *10*)

Patient	Age (yr)	Level of catheter	Extradural morphine	Parenteral opiates	Clinical course	Comment
1	27	Lumbar	4 mg immediately after anaesthesia.	Neuroleptanaesthesia	Ventilatory depression within 30 min after extradural morphine. Naloxone given once.	Ventilatory depression induced by extradural morphine given early after neuroleptanaesthesia.
2	52					
3	58	L3–4	4 mg × 3 within 19 h, last dose immediately before bronchoscopy.	In low doses as premedication and during bronchoscopy.	Ventilatory depression 5 h after last dose of extradural morphine. Naloxone given once.	Ventilatory depression induced by concomitant use of extradural and parenteral opiates in a patient with chronic bronchitis.
4	>70	?	Probably 2 mg immediately after anaesthesia.	Probably 5 mg of morphine within 30 min after the extradural dose.	Ventilatory depression within 30 min after parenteral morphine. Naloxone given once.	Ventilatory depression induced by concomitant use of extradural and parenteral morphine in early postop. period.
5	>70					
6	>70	Th8–9	2 mg immediately after anaesthesia.	Neuroleptanaesthesia.	Ventilatory depression within 30 min after extradural morphine. Naloxone given once.	Ventilatory depression induced by extradural morphine given early after neuroleptanaesthesia.
7	>70	Th9–10				
8	75	Lumbar	Morphine 20 mg 30–60 min after anaesthesia.	Low doses of opiates as premedication and during operation.	Ventilatory depression requiring naloxone 12 h after extradural dose. After 6 h, 6–10 b.p.m.	Late ventilatory depression after a high extradural dose of morphine.
9	77	Th9–10	4 mg × 3 within 7 h, first dose 0.5 h after anaesthesia. Repeated doses on 1st and 2nd postop. day.	Low doses of opiates during total gastrectomy.	Ventilatory depression 8 h after last extradural dose. Naloxone administered twice within 1.5 h.	Late ventilatory depression after repeated doses of extradural morphine.
10	78	Th8–9	Morphine 2 mg 25 min after anaesthesia.	Neuroleptanaesthesia.	Ventilatory depression 3 h after extradural dose. Naloxone given once.	Ventilatory depression induced by extradural morphine given early after neuroleptanaesthesia.

TABLE II. *Patients with ventilatory depression (extradural morphine given 1 h or later after anaesthesia (n = 9). Patient No. 13 reported by Gustafsson, Feychting and Klingstedt (1981); No. 14 by Reiz and Westberg (1980); No. 18 by Modig and Paalzow (1981)*

Patient	Age (yr)	Level of catheter	Extradural morphine	Parenteral opiates	Clinical course	Comment
11	49	L1–2	4 mg 5 h after anaesthesia.	1.2 mg of leptanal during thoracotomy, moderate doses of opiate i.m. 2.5 and 6 h after anaesthesia.	Ventilatory depression 6.5 h after extradural morphine and 2 h after last parenteral dose of opiate. Dura perforation (L2–L3).	Ventilatory depression after concomitant use of extradural and parenteral opiates in a patient with dura perforation.
12	66	L3–4	4 mg × 2 within 3 h, first dose 7 h after anaesthesia.	None, except a small dose as premedication.	Ventilatory depression 3 h after last extradural dose. Naloxone given once.	Ventilatory depression 3 h after a repeated dose of extradural morphine.
13	68	Th7–8	2 mg × 3 within 1 h, first dose 2 h after anaesthesia.	Small doses of opiates during operation, morphine 10 mg s.c. 3 h after last extradural dose.	Ventilatory depression 5h after parenteral morphine. Naloxone given once.	Ventilatory depression 8 h after the first extradural dose of morphine and induced by concomitant use of extradural and parenteral morphine.
14	70	Thoracic	2 mg 2.5 and 12.5 h after anaesthesia.	Small dose of opiate as premedication.	Ventilatory depression 4 and 4.3 h after second dose. Naloxone given twice within 20 min.	Ventilatory depression after repeated small doses of extradural morphine.
15	70	Lumbar	Morphine 5 mg 1 h after anaesthesia.	A moderate dose of a parenteral opiate about 8 h after extradural dose.	Ventilatory depression about 9 h after the extradural and 1 h after a parenteral dose of opiate.	Ventilatory depression induced by concomitant use of extradural and parenteral opiates.
16	75	Lumbar	4 mg about 4 h after anaesthesia.	None except a small dose as premedication.	Ventilatory depression requiring naloxone 6 and 9 h after the dose.	Ventilatory depression 6 and 9 h after a single extradural dose of morphine.
17	75	L2–3	Morphine 2 mg 5 h after anaesthesia.	Small dose of opiate as premedication and 10 mg of morphine s.c. 3 h after extradural morphine.	Ventilatory depression 9 h after the extradural dose. Naloxone repeated twice within 4 h.	Ventilatory depression after concomitant use of extradural and parenteral morphine.
18	78	Th7–8	Morphine 5 mg 10 and 20 h after anaesthesia.	0.8 mg of leptanal during op. of aortic aneurysm.	Ventilatory depression requiring naloxone once 6 h after last dose of extradural morphine.	Ventilatory depression after two repeated injections of extradural morphine.
19	79	L3–4	3 mg 7 h after anaesthesia.	Small doses of opiates as premedication and 10.5 h after anaesthesia.	Ventilatory depression 7.7 h after extradural morphine. Naloxone given four times within 3 h.	Ventilatory depression induced by concomitant use of extradural and parenteral opiates in a septic patient.

TABLE III. *Patients with cancer or trauma experiencing ventilatory depression after extradural morphine* (n = 4)

Patient	Age (yr)	Level of catheter	Extradural morphine	Parenteral	Clinical course	Comment
20	55–60	Thoracic	Morphine 2 mg	24 h before extradural morphine, moderate doses of opiates in parenteral form because of rib fractures.	Within 30 min after extradural morphine, ventilatory depression. Naloxone given once.	Ventilatory depression after a small extradural dose of morphine in a patient given moderate systemic doses of opiates and with multiple rib fractures.
21	68	Thoracic	Morphine 2 mg	During 4 h before extradural morphine, high doses of parenteral opiates to treat pain caused by rib fractures.	Within 30 min after extradural morphine, ventilatory depression. Naloxone given once.	Ventilatory depression after a small extradural dose of morphine in a patient given repeated systemic doses of opiates and with multiple rib fractures.
22	72	Thoracic	Morphine 2 mg	Two high doses of parenteral opiates 1–2 h before extradural morphine.	Within 30 min after extradural morphine, ventilatory depression. Naloxone given once.	Ventilatory depression after a small extradural dose of morphine in a patient given repeated systemic doses of opiates and with multiple rib fractures.
23	75	Lumbar	Day 1: 2 mg × 2, sacral route. Days 2–3: 2 mg × 3, lumbar route. Days 4–11: 1 mg × 3.	Day 3: single doses of parenteral opiates. Days 8–11: methadone orally, doses not known.	Day 11 unconscious, ventilatory depression, one dose of naloxone. After cessation of extradural and oral doses of opiates, pain free for 1 week.	Ventilatory depression induced by accumulation of methadone in a patient concomitantly treated with extradural morphine.

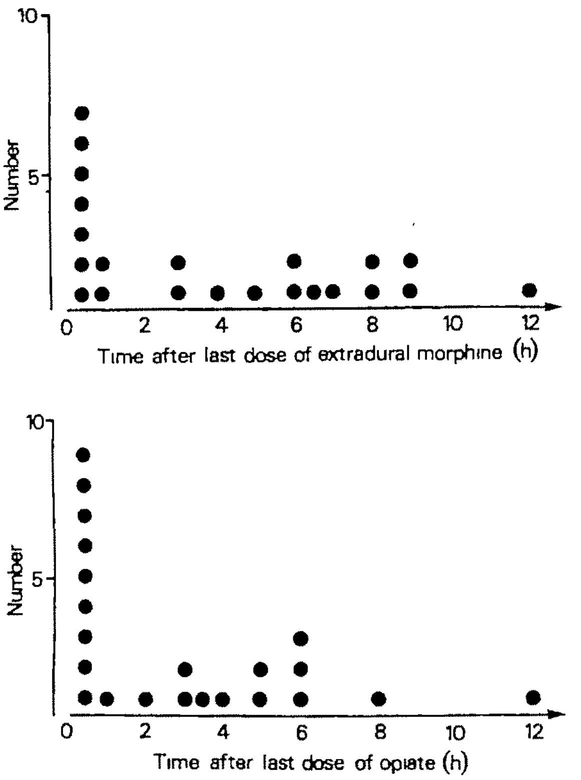

FIG. 2. Hours between the administration of the last dose of extradural morphine (upper legend) and the last dose of opiates (s.c., i.m , i.v. or extradural) (lower legend) and the occurrence of ventilatory depression requiring naloxone (22 patients).

Severe pruritus. Severe pruritus after extradural morphine was reported by 18 departments. Six reported a frequency less than 2%, two between 2 and 5% and six a frequency greater than 5%.

Urinary retention. The stated frequency of patients requiring bladder catheterization varied from 0.3 to 25% with a median value of 10%.

Other adverse effects. Neurological sequelae after administering morphine were not observed. Reports of single patients experiencing nausea or vomiting euphoria, anxiety or hallucinations were obtained from 11 departments.

One patient, 78 yr of age, underwent transurethal diathermy resection of the prostate under extradural anaesthesia with mepivacaine. Three hours after anaesthesia he was given a single dose of morphine 2 mg. Ten to 20 minutes after that injection the patient hallucinated, shivered and became unconscious. The respiratory rate, arterial pressure and heart rate, and the electrolyte concentrations in plasma were normal. The symptoms disappeared within 5–10 min without treatment.

Use of intrathecal opiates

Of the 10 departments in which intrathecal morphine was used only three were still using the method. Between 90 and 150 patients had been treated.

Six departments had observed adverse effects, the most frequent being ventilatory depression. After 0.8–2.0 mg of extradural morphine before cholecystectomy or total hip replacement, six of 32 patients developed $P\text{CO}_2$ greater than 7 kPa more than 8 h after anaesthesia. Five of these patients received naloxone. In 10 of the 12 that underwent cholecystectomy the lungs were artificially ventilated for at least 1.5 h after operation. (These 32 patients have been reported by Gjessing and Tomlin (1981).) One patient undergoing transvesical prostatectomy developed ventilatory depression 8 h after morphine 4 mg. He required repeated doses of naloxone for 8 h and thereafter artificial ventilation for another 12 h.

DISCUSSION

In 1976 a study on the effectiveness of intrathecal morphine for relief of experimental pain in rats was published (Yaksh and Rudy, 1976). This report initiated a series of trials in man in which long lasting pain relief (24–36 h) was observed after small doses of extradural or intrathecal morphine (Bahar et al., 1979; Wang, Nauss and Thomas, 1979). The use of these methods spread rapidly (Editorial, 1980) and became clinically accepted long before data from controlled studies were published.

Our survey further supports the impression of widespread use of these methods in clinical practice. Three years after publication of the original animal study (Yaksh and Rudy, 1976) a majority of the departments of anaesthesia in Sweden had used opiates extradurally.

The standard dose of morphine for extradural use was similar among different departments with a tendency to use smaller doses when the drug was given at the thoracic level. It is, however, not known if it is optimal to treat different postoperative pain conditions with the same standard dose. The infrequent use of morphine extradurally for obstetric pain may be attributed to the disappointing clinical results (Husemeyer, O'Connor and Davenport, 1980; Nybell-Lindahl et al., 1981). Our results underline the necessity to perform controlled clinical studies to define the dose and schedule of administration of morphine extradurally under different pain conditions.

Late ventilatory depression was reported in 4–7% of patients treated with intrathecal morphine. Higher figures have been reported in prospective studies (Davies, Tolhurst-Cleaver and James, 1980; Gjessing and Tomlin, 1981). Interestingly, in one recent study none of 440 patients developed ventilatory depression when 0.3 or 0.4 mg of morphine was administered intrathecally for postoperative pain relief (King et al., 1981). Thus, it may be possible to decrease the occurrence of ventilatory depression by administering smaller doses.

This is the largest survey so far reported on ventilatory depression after extradural morphine. This potentially life-threatening side-effect was reported in 0.25–0.40% of the patients in our sample. However, this figure is certainly an underestimate as the study was retrospective.

Nine of the 22 patients who developed ventilatory depression within 1 h after the last dose of extradural morphine received both extradural and systemic doses of opiates. Even if the concentration of morphine is reported to be small in plasma after extradural administration, it may induce ventilatory depression when a systemic dose of opiate is administered concomitantly (Weddel and Ritter, 1981).

Five of seven patients who developed ventilatory depression later than 6 h after the last dose of extradural morphine (patients Nos 11, 13, 15, 17, 19) received systemic doses of opiates also. Restricted use of systemic opiates when patients are treated with extradural morphine may reduce the risk of this dangerous late ventilatory depression (Boas, 1980; Reiz and Westberg, 1980; Gustafsson, Feychting and Klingstedt, 1981).

Other risk factors seemed to be an age of 70 yr or more, impaired respiratory function (patients Nos 3, 20–22) and thoracic administration. Only two of 22 patients developed depression later than 6 h after opiate administered by any route. In these cases (patients Nos 8, 17) high doses of morphine were given (tables I, II). This indicates that the extradural administration of morphine is reasonably safe if certain clinical factors are taken into consideration. More than 6 h after the last opiate administration (s.c., i.m., i.v. or extradural), the risk of ventilatory depression was greatly reduced. This does not mean that it is safe to give a further dose of opiate systemically more than 6 h after the last dose of extradural morphine. One patient developed respiratory depression when morphine was given systemically 8 h after the last extradural dose.

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EFFETS DELETERES DES OPIACES ADMINISTRES PAR VOIE SOUS- ET PERIDURALE: RESULTATS D'UNE ENQUETE NATIONALE EN SUEDE

RESUME

La Société Suédoise d'Anesthésiologie a mené une enquête nationale rétrospective sur l'expérience clinique de l'utilisation sous- et péridurale des opiacés. Une attention toute particulière s'est portée sur la fréquence et le type de la dépression respiratoire. Quatre-vingt-quatre-départements sur 93 ont répondu au questionnaire (90%). Jusqu'au mois de mai 1981, de la morphine a été administrée par voie péridurale à environ 6000–9150 patients, de la péthidine par voie péridurale à 220–450 patients et de la morphine intrathécale à 90–150 patients. Une dépression respiratoire nécessitant un traitement par la naloxone a été décrite chez 23 patients traités par la morphine pa voie péridurale (0,25–0,40%) et chez six patients traités par la morphine par voie intrathécale (4–7%). Chez 22 patients, l'administration de morphine par voie péridurale a été considérée comme un facteur principal ou aggravant de survenue d'une dépression respiratoire. Seuls deux patients parmi ces 22 ont objectivé cette dépression respiratoire plus de 6 h après la dernière dose d'opiacé (s.c., i.m., i.v. ou péridurale). Il semble y avoir eu une sur-représentation de patients de 70 ans et plus, de patients ayant subi une analgésie péridurale dorsale et de patients ayant une capacité respiratoire diminuée.

GEFÄHRLICHE NEBENWIRKUNGEN VON PERIDURALER UND INTRATHEKALER ANWENDUNG VON OPIATEN: BERICHT ÜBER EINE LANDESWEITE RETROSPEKTIVE UNTERSUCHUNG IN SCHWEDEN

ZUSAMMENFASSUNG

Die Schwedische Gesellschaft für Anästhesie führte eine landesweite retrospektive Untersuchung über die klinischen Erfahrungen mit der epiduralen und intrathekalen Verabreichung von Opiaten durch. Das besondere Interesse galt der Häufigkeit und der Art einer dabei auftretenden Atemdepression. Den Fragebogen beantworteten 84 von 93 Abteilungen (90%). Bis zum Mai 1981 hatten 6000 bis 9150 Patienten Morphium epidural, ca. 220 bis 450 Patienten epidural Pethidin und 90 bis 150 Patienten intrathekal Morphium erhalten. Über das Auftreten einer Atemdepression, die Behandlung mit Naloxon erforderlich machte, wurde bei 23 Patienten, denen epidural Morphium 0,25–0,40% und bei 6 Patienten, denen intrathekal Morphium 4–7% verabreicht worden war, berichtet. Bei 22 Patienten nahm man an, daß die Verabreichung von epiduralem Morphium den hauptsächlichen oder einen zusätzlichen Faktor für das Auftreten einer Atemdepression darstellte. Nur zwei von diesen 22 Patienten hatten später als 6 Stunden nach der letzten Opiatdosis (s.c., i.m., i.v od epidural) eine Atemdepression. In der Gruppe mit Atemdepression befanden sich vermehrt Patienten, die 70 Jahre oder älter waren, oder bei denen eine Epiduralpunktion in der Thorakalregion durchgeführt worden war oder solche mit eingeschränkter Lungenfunktion.

EFECTOS ADVERSOS DE LOS OPIATOS EXTRADURALES E INTRATECALES: INFORME DE UN ESTUDIO EFECTUADO EN SUECIA A ESCALA NACIONAL

SUMARIO

La Sociedad Sueca de Anestésicos ha llevado a cabo un estudio restrospectivo a nivel nacional al respecto de las experiencias clínicas con los opiatos de administración extradural e intratecal. Se emplazó un interés especial sobre la frecuencia y el tipo de depresión respiratoria. El cuestionario lo contestaron 84 de los 93 departamentos contactados (90%). Hasta el mes de mayo de 1981 se había administrado morfina extradural a entre 6000 y 9150 pacientes, petidina extradural a entre 220 y 450 pacientes y morfina intratecal a entre 90 y 150 pacientes. Se informó el uso de naloxano como tratamiento de la depresión respiratoria en 23 pacientes tratados con morfina extradural (0,25–0,40%) y en seis a los que se les administró morfina intratecal (4–7%). En 22 de los pacientes la administración de morfina extadural se consideró como un factor principal o contribuyente a la aparición de depresión respiratoria. Tan sólo dos de los 22 pacientes experimentaron depresión respiratoria después 6 horas de haber administrado la última dosis de opiatos (subcutánea, intramuscular, intravenosa o extradural). Parece ser excesiva la representación de pacientes de edad igual o superior a los 70 años, la de aquellos que recibieron inyección toráctica extradural y la de aquellos con capacidad ventiladora reducida.

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ABSTRACTS

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The corresponding author has, where appropriate, certified that studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

Effects of methylnaltrexone on chronic opioid-induced gut motility and transit time changes

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Morphine and other opioids are widely used analgesics in patients with advanced cancer, and in this population the most common side effect of opioid medications is constipation.[1] For those patients requiring increasing doses of opioids for their pain, the conventional measures for opioid-induced constipation are often insufficient, and constipation becomes a limiting factor in opioid use and opioid dose.[1] Methylnaltrexone (MNTX) is a novel quaternary ammonium opioid receptor antagonist that does not cross the blood–brain barrier.[2] It offers a therapeutic potential of decreasing the peripheral gut side effect of opioids while preserving analgesia. In normal volunteers, both i.v. and oral MNTX effectively blocked acute morphine-induced delay in oral–caecal transit time using the lactulose hydrogen breath test.[3 4] Recently, we observed a significant delay of the transit time in patients with long-term methadone dependence. This delay, corresponding to a significant increase in complaints of constipation, suggests that chronic opioid use does not induce tolerance in the gut. Before using MNTX in chronically ill cancer patients we performed this pilot study, in which gut effects of i.v. MNTX were evaluated in patients receiving long-term methadone therapy as a proxy group for patients with chronic pain, to observe if these individuals were more or less sensitive to the compound.

With approval from the Institutional Review Board, two men and two women with opioid-induced constipation as a result of long-term methadone therapy were admitted to the Clinical Research Center. They received placebo the first day, then i.v. MNTX (0.05–0.45 mg kg^{-1}) was given twice daily for the rest of the week in a single-blind protocol. Oral–caecal transit time was recorded, as well as laxation response on the basis of the frequency and consistency of stools during the study period. Pharmacokinetic data were collected and analysed.

Two individuals who received an MNTX dose of 0.45 mg kg^{-1} (a dose previously used in volunteers) showed immediate positive laxation with i.v. infusion. One of them had severe abdominal cramping, but showed no other signs of systematic withdrawal such as lacrimation, diaphoresis, mydriasis or hallucinations. In the other two subjects, MNTX dose was reduced to 0.05–0.15 mg kg^{-1}. These latter two subjects also had an immediate laxation response during and after i.v. medication, with mild abdominal cramping. Their stool frequency increased from two to three per week before the study to 1.75 per day during the treatment period. Gut transit times were reduced from 150 min (baseline) to 60 min (at the end of the study) for each subject.

Our preliminary results demonstrated that low-dose i.v. MNTX effectively reversed opioid-induced constipation and delay in gut transit time in long-term users of methadone. We therefore expect that cancer patients receiving prolonged treatment with opioids may also have increased sensitivity to MNTX, and that low-dose MNTX may be clinically useful in managing opioid-induced constipation. The studies of MNTX could potentially improve pain management in patients with chronic pain.

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Opioid requirement during surgery for Crohn's disease

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A previous study[1] demonstrated an increased requirement for opioids in patients with Crohn's disease. This was attributed to a change in opioid pharmacodynamics without any change in pharmacokinetics. The aim of this study was to evaluate whether the inflammatory process as reflected by erythrocyte sedimentation rate (ESR) influences opioid requirement during abdominal surgery.

With their informed consent, we studied 16 patients with Crohn's disease scheduled for abdominal surgery (bowel resection). Patients were allocated into group A (n = 6), in which ESR was normal (< 20 min) or group B (n = 10), in which ESR was > 20 min. Anaesthesia was induced with sufentanil 0.5 μg kg^{-1} and propofol, and maintained with 50% nitrous oxide in oxygen, isoflurane, and continuous infusion of sufentanil at 0.3 μg kg^{-1} h^{-1}. Additional boluses of sufentanil were given and the infusion rate increased when haemodynamic variables increased by up to 20% of the preoperative values. Mean intraoperative sufentanil requirement was measured during four stages of the operation: time from induction to incision ($T1$), to retractors set ($T2$), to bowel resection ($T3$), and to end of surgery ($T4$). C-reactive protein, Crohn's disease activity index (CDAI), length of bowel resection and serum albumin levels were collected. Data (mean (SEM)) were analysed by Student's t test, and stepwise regression analysis; P < 0.05 was considered significant.

There were no differences between the two groups in patient characteristics, ASA classification, duration of surgery or length of bowel resection. Mean intraoperative sufentanil requirement was significantly greater in group B (1.37 (0.22) vs 0.62 (0.11) μg kg^{-1} h^{-1}). During $T1$, there were no differences between the two groups (fig. 1). During $T2$ a greater opioid requirement was noted in group B (4.42 (1.05) *vs* 0.55 (0.14) μg kg^{-1} h^{-1}). During $T3$, sufentanil requirement remained elevated in group B, but this was not significant during $T4$. Concentrations of C-reactive protein and serum albumin and CDAI were not significantly different between the two groups. There was a significant correlation (r^2 = 0.315) between sufentanil consumption and ESR (P = 0.02).

In patients with Crohn's disease, the systemic inflammatory state of the disease as reflected by ESR (but not by C-reactive protein) seems to be a predictive factor for opioid requirement during bowel resection.

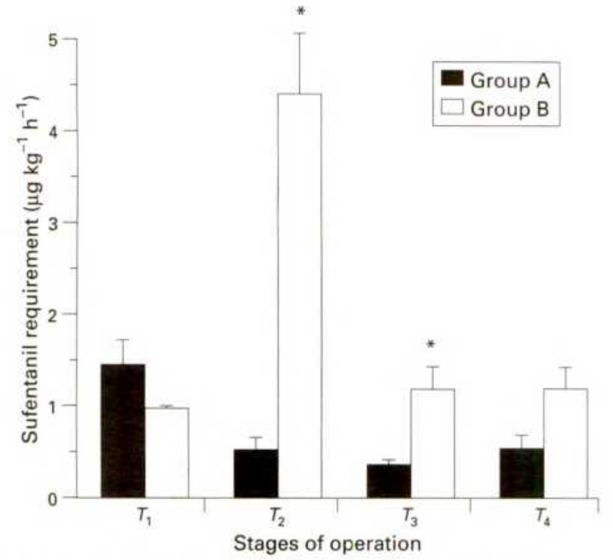

Figure 1 Requirement for opioid (sufentanil) during bowel resection for Crohn's disease. Group A ($n = 6$), ESR < 20 min; Group B ($n = 10$), ESR > 20 min; *T1*, *T2 T3*, *T4*, stages of operation (see text). $^{\star}P < 0.05$ between groups.

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The role of C-tail in opioid receptor down-regulation

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Prolonged exposure to opioid peptides and opiate alkaloids causes down-regulation of the opioid receptors. Receptor degradation has been implicated in this down-regulation process. Loss of receptor binding sites after prolonged opioid treatment has been demonstrated previously using whole animals and cell lines expressing opioid receptors. We have used Chinese hamster ovary cells stably expressing δ opioid receptors to examine the domains of the receptor involved in down-regulation, and found that the receptor C-tail plays an important part in receptor down-regulation.[1,2] A single-point mutation (Thr353 to Ala) in the C-tail of mouse δ opioid receptor blocks substantially receptor down-regulation.

To evaluate critically the role of Thr353 in the down-regulation process, a chimeric receptor was generated where the C-tail of mouse δ opioid receptor was replaced by the C-tail of rat δ opioid receptor, which contains a naturally occurring Ala353. This mouse/rat chimeric receptor was expressed in Chinese hamster ovary cells and its long-term down-regulation was measured by treating the cells with 100 nM [D-Ala2, D-Leu5]-enkephalin (DADLE) or 100 nM DADLE + 1 µM naloxone at 37 °C for 1–7 days. After extensive washing with buffer, ^{3}H-diprenorphine binding to whole cells was measured and analysed as described previously.[1]

We find that the chimeric receptor exhibits long-term down-regulation in response to agonist treatment, and this effect is antagonized by the presence of 1 µM naloxone (fig. 2). These results suggest that the information for down-regulation is contained within the C-tail, and that the absence of Thr353 in the chimeric receptor is partially compensated by other residues in the C-tail. Taken together, the data underscore the importance of receptor C-tail in regulating receptor degradation.

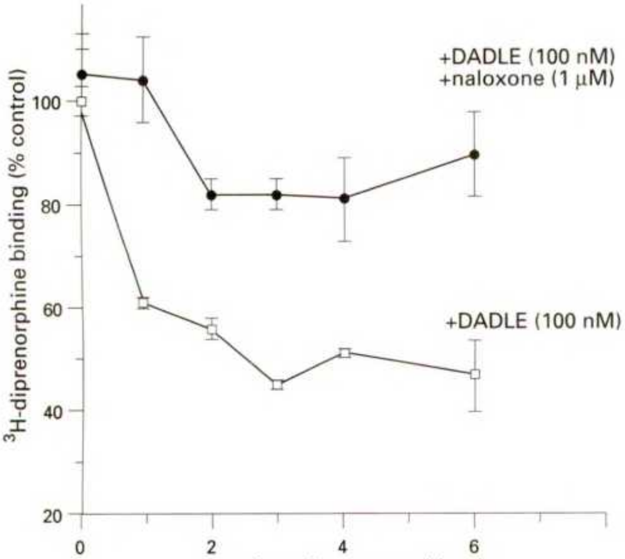

Figure 2 Treatment with an opioid agonist (DADLE) caused long-term down-regulation of a mouse/rat chimeric δ opioid receptor. Values are the mean (SEM) of three determinations.

Supported by grants DA08863 and NS01788.

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Effects of C-terminal truncation of the δ opioid receptor on [D-Pen^{2,5}-]enkephalin (DPDPE) stimulated increases in intracellular calcium

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We have previously shown that the recombinant δ opioid receptor expressed in Chinese hamster ovary (CHO) cells couples to Phospholipase C (PLC),[1] and causes an increase in intracellular calcium.[2] In addition, the δ opioid receptor-PLC coupling may be affected by removal of the C–terminus of the receptor.[1] In this study we examine the effect of removal of the C–terminus on DPDPE-stimulated increases in intracellular calcium ($[Ca^{2+}]_i$).

CHO cells expressing either δ opioid receptor (δOR) or δ opioid receptor with the C-terminus truncated by 37 amino acids (δOR37) were maintained in supplemented Hams F12 medium. $[Ca^{2+}]_i$ was measured fluorimetrically in Fura-2 loaded suspensions of whole cells in Krebs-HEPES buffer, pH 7.4 as described previously.[3] All data are presented as mean (SEM); $n = 4$.

DPDPE produced a dose-dependent and naloxone-reversible increase in $[Ca^{2+}]_i$ in both the δOR and δOR37 clones with pEC_{50} values of 8.53 (0.09) (2.95 nM) and 5.48 (0.13) (3.31 µM) respectively. In both cell types the maximum peak phases were similar (δOR = 112 (22) nM, δOR37 = 95 (10) nM) and were from IP_3-sensitive stores, because pretreatment with thapsigargin abolished the DPDPE-induced increase. In the absence of extracellular calcium the increase was monophasic. When extracellular calcium was replaced an increase in $[Ca^{2+}]_i$ was observed. However, part of the increase was Mn^{2+} quenchable, possibly indicating Fura-2 leakage. The κ agonist spiradoline (1 µM δOR, 30 µM δOR37) and the µ agonist [D-Ala^2,MePhe^4,gly(ol)]enkephalin (1 µM δOR, 30 µM δOR37) were ineffective.

These data show that the recombinant δ opioid receptor expressed in CHO cells increases intracellular calcium and that C-terminal deletion produces a marked rightward shift in the dose–response curve. We are examining the mechanism or mechanisms responsible for this difference and the nature of the plateau-phase increase in $[Ca^{2+}]_i$.

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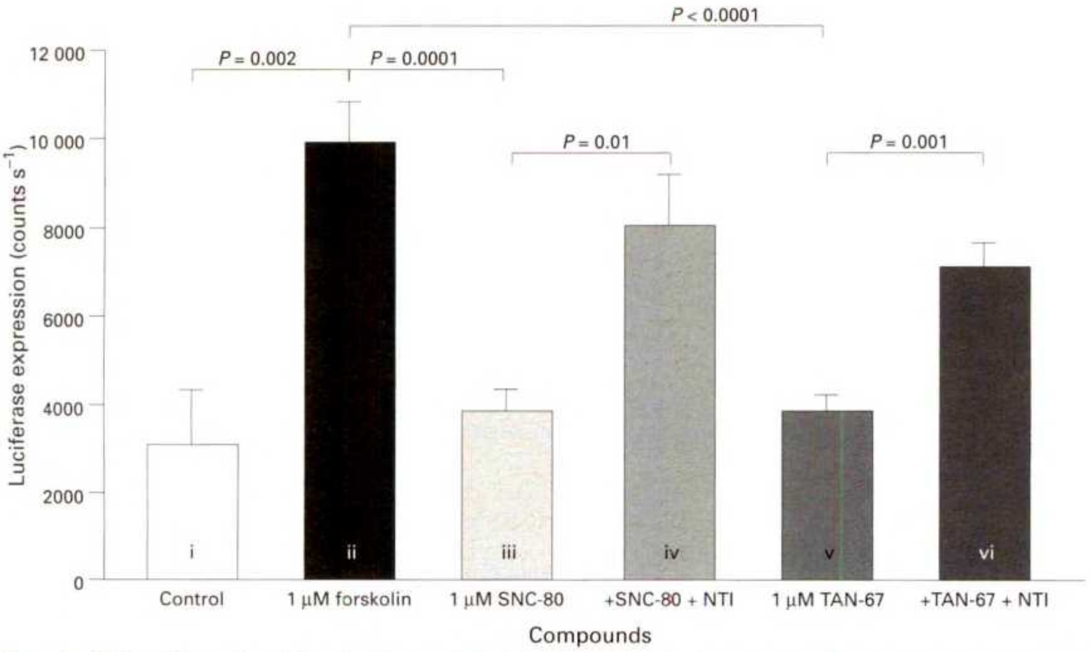

Figure 3 Effect of δ-agonists with and without naltrindole (NTI) on forskolin-stimulated luciferase expression in VIPluc-transfected δC6-CHO cells.

Use of transcriptional control of a reporter gene as a measure of δ opioid receptor activation

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The aim of this study was to investigate the potential of using the transcriptional control of reporter-gene expression, by cAMP response elements, as a measure of human δ opioid receptor (hDOR) activation, in a recombinant cell line.

The hDOR cDNA was obtained from B. Kieffer (Strasbourg) and subcloned into the mammalian expression vector pcDNA3. A Chinese hamster ovary (CHO) cell line expressing the hDOR was generated (clone δC6). When expressed, hDOR demonstrated the binding characteristics typical of a δ opioid receptor. The δC6 cell line was transiently transfected with the plasmid VIPluc (pGL2-c6-c4-VIPprom: pGL2-Control Vector containing the luciferase gene and the VIP promoter under the control of 11 cAMP response elements (CREs)), using Lipofectamine, on day 1. On day 3, the cells were replated into white, opaque 96-well plates at 30 000 cells per well. On day 4, the cells were used in the experiment. To the 200 μl of medium in each well was added 20 μl of vehicle (deionized water containing 1% DMSO) containing the following compounds (final assay concentrations are indicated): (i) control (vehicle only); (ii) 1 μM forskolin; (iii) 1 μM forskolin + 1 μM SNC-80; (iv) 1 μM forskolin + 1 μM SNC-80 + 50 μM naltrindole; (v) 1 μM forskolin + 1 μM TAN-67; (vi) 1μM forskolin + 1 μM TAN-67 + 50 μM naltrindole. The cells were incubated for 5 h at 37°C in 5% carbon dioxide before assaying for luciferase expression using LucLite (Packard) and a 96-well plate luminometer (TopCount, Packard). Data are represented as mean of 12 wells (SEM), from one experiment; *P* values were calculated using a single-tail *t* test.

Preliminary results indicate that the non-peptide DOR agonists SNC-80 and TAN-67, inhibit forskolin-stimulated increases in expression of the reporter gene (luciferase) (fig. 3). This effect was partially reversed by the δ opioid receptor antagonist naltrindole. We presume that the effects of these agonists were mediated via an inhibition of adenylate cyclase, via G-protein activation. However, this has yet to be confirmed. If this assay proves to be robust, it may provide a means by which the relative potencies of compounds at the hDOR can be rapidly assessed.

A comparison of PCA pethidine, nalbuphine and tramadol for anaesthesia-free extracorporeal shock wave lithotripsy

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Second-generation lithotripters offer immersion-free extracorporeal shock wave lithotripsy (ESWL) with less shock wave energy.[1] Consequently, general or extradural anaesthesia is not always needed.[2 3] In this controlled, randomized double-blind study we compared the analgesic efficacy of pethidine, nalbuphine and tramadol during ESWL.

We studied 90 patients (ASA I or II) undergoing ESWL for renal calculi using a Dornier MFL 5000 lithotripter. Patients were assigned to receive pethidine ($n = 30$), nalbuphine ($n = 30$) or tramadol ($n = 30$) administered by patient-controlled analgesia (PCA). The use of PCA was explained to patients at the preoperative visit, as was the visual analogue scale (VAS) for indication of pain experienced. Premedication consisted of diclofenac 100 mg rectally and metoclopramide 10 mg orally 1.5 h before ESWL. The analgesic drugs were prepared in identical 10 ml syringes, containing pethidine (10 mg ml^{-1}), nalbuphine (2 mg ml^{-1}) or tramadol (10 mg ml^{-1}). Monitoring consisted of ECG, heart rate, non-invasive arterial pressure, respiratory rate and continuous percutaneous oxygen haemoglobin saturation (Sp_{O_2}). All patients received oxygen 6 litre min^{-1} by face mask. A 2 ml bolus of the analgesic drug was given before ESWL, after which patients could receive a 1 ml bolus on demand, with a lock-out interval of 5 min. Treatment was begun at 18 kV and gradually increased to 26 kV if tolerated. After the procedure the patients were asked whether they would choose the same analgesia if they needed the treatment again. Results were analysed by ANOVA and the chi-square test using SPSS statistical software. All results are presented as mean (SD). $P < 0.05$ was considered significant.

One patient each in the nalbuphine and pethidine groups refused to continue with the treatment because of unbearable pain. One patient in the tramadol group developed hypertension that required i.v. hypotensive drugs and abandonment of ESWL. There was no significant difference between the groups with regard to VAS, time to first demand for analgesia or satisfaction with the analgesia (table 1). Heart rate, blood pressure, respiratory rate and Sp_{O_2} were not different between the groups. There were no cases of hypotension or respiratory depression.

Table 1 Efficacy of three drugs used for patient-controlled analgesia during extra corporeal shock wave lithotripsy (ESWL). VAS 1 = visual analogue scale halfway through ESWL; VAS 2 = visual analogue scale at the end of ESWL

	Pethidine	Nalbuphine	Tramadol
VAS 1	35.13 (23.9)	27.45 (23.9)	41.21 (20.9)
VAS 2	40.79 (22.8)	39.24 (22.0)	41.93 (19.1)
Time to first demand (min)	12.41 (6.1)	11.43 (7.1)	9.48 (6.6)
Same analgesia again (%)	69	57	38

We conclude that although the highest VAS scores, the shortest time to first demand and the least satisfaction were recorded for the tramadol group, all three analgesic drugs studied can be used effectively and safely for anaesthesia-free ESWL treatment for renal calculi.

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The effect of remifentanil upon the hypertensive response to orotracheal intubation

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The aim of this study was to assess the effect of remifentanil upon the cardiovascular response to intubation and the effect of concurrent administration of glycopyrrolate.

We studied 40 ASA I–II female patients aged 18–48 yr presenting for elective surgery. Ten patients were assigned in a randomized, double-blind fashion to each of four treatment groups: remifentanil (bolus, 1 μg kg^{-1}, then infusion, 0.5 μg kg^{-1} min^{-1}); saline placebo only; glycopyrrolate (200 μg) and remifentanil (bolus, 1 μg kg^{-1}, then infusion, 0.5 μg kg^{-1} min^{-1}) and glycopyrrolate (200 μg) only. This was followed by a standard general anaesthetic technique consisting of propofol (titrated to sleep dose), vecuronium (0.1 mg kg^{-1}) and 1% isoflurane with 70% nitrous oxide in oxygen. Arterial pressure was measured non-invasively by an automatic oscillometric device (Datex Cardiocap) and heart rate from the ECG trace. Intubation was performed after 3 min. Observations were recorded every minute from the start of induction to 5 min after intubation.

There was no significant difference between the four groups (ANOVA) with respect to age, weight, pre-anaesthetic mean arterial pressure (MAP) and heart rate. The remifentanil groups required less propofol than the non-remifentanil groups ($P = 0.01$, paired t test). In the non-remifentanil groups a significant increase in MAP and heart rate at intubation were evident. Five patients in the remifentanil group and one in the remifentanil and glycopyrrolate group displayed bradycardia (heart rate < 45 min^{-1}) or hypotension (systolic arterial pressure < 80 mm Hg) or both, that required rescue measures to be taken. Analysis of MAP over the nine time-points showed a highly significant difference between groups (MANOVA). Data from three of the nine time-points are shown in table 2.

These results suggest that remifentanil attenuates the hypertensive response to intubation but patients may require pretreatment with a vagolytic agent if concurrent bradycardia and hypotension are to be avoided. A lower dose of remifentanil might be adequate.

The effect of nociceptin, nociceptin analogues and a novel hexapeptide agonist at the ORL-1 receptor in central and peripheral sites

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Nociceptin (orphanin FQ) is the endogenous ligand for the ORL-1 receptor. Transcripts for the ORL-1 receptor have been shown to exist in the central nervous system and in some peripheral areas including the vas deferens.

We have shown that nociceptin is a potent and efficacious agonist in the vas deferens of the rat (RVD) and rabbit[1] and have characterized the binding of [^{3}H]-nociceptin at the ORL-1 receptor site in guinea-pig, rabbit and rat brain membranes[2] We have tested some analogues of nociceptin in the vas deferens and in radioligand binding studies and have begun behavioural studies with these compounds after intracerebroventricular (i.c.v.) administration in the rat.

Hooded Lister rats (weighing ~300 g) were implanted with cannulae into the right lateral ventricle under isoflurane anaesthesia. The coordinates for cannula implantation (mm), measured from Bregma, were: 1.5 lateral, 0.8 caudal and 3.2 ventral from the surface of the skull. Animals were housed individually and allowed 1 week to recover before use. I.c.v. injections were in a volume of 2 μ litre, administered over 30 s. Animals were placed in a new environment, video monitored for 1 h and then scored for horizontal locomotion and rearing behaviour.

I.c.v. administration of nociceptin (5 nmol, $n \geq 6$) produced a decrease in horizontal locomotor activity and rearing when compared with vehicle controls ($P < 0.05$). Administration of this dose of nociceptin was associated with an impairment of motor function that was confined to the hind limbs. Nociceptin (2–17) (5 nmol, $n = 9$) did not alter horizontal locomotion and rearing behaviours and the nociceptin-induced motor impairment was not evident. This lack of effect is consistent with data obtained from the rat vas deferens where nociceptin(2–17) was found to be inactive as an agonist at concentrations up to 3 μM ($n = 3$) and in radioligand binding studies with [^{3}H]-nociceptin where it was inactive up to 10 μM ($n = 3$).

Screening of hexapeptides from combinatorial libraries has led to the identification of the potent agonist action of Ac.RYYRWK.NH$_2$ at ORL-1.[3] In the RVD this compound was more potent than nociceptin itself (EC$_{50}$ values 0.8 nM, range 0.75–0.89, and 7.88 nM, 6.99–9.24, n=6), although not as efficacious (E$_{max}$ 0.71 (0.02) and 0.94 (0.09)). When tested in radioligand binding studies the novel hexapeptide was found to have as high an affinity for the ORL-1 receptor as nociceptin (pK$_i$ 9.94 (0.21), $n = 5$ and 9.96 (0.16), $n = 8$ respectively). However, when this novel hexapeptide was administered i.c.v. to rats (5 nmol, $n = 6$) it did not alter the locomotor or rearing behaviour of the animals when compared with vehicle-treated controls.

Thus, we have shown nociceptin to be a high-affinity ligand of the ORL-1 receptor in the brain and vasa deferentia. Further to this, i.c.v. administration of nociceptin has been shown to decrease locomotor activity through a mechanism that remains to be elucidated. Although radioligand binding studies have shown the novel hexapeptide displaying high affinity for ORL-1 and we have found it to be a potent agonist in the RVD, we did not observe a nociceptin-like reduction in locomotor activity following i.c.v. administration in rats

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Table 2 Effect of remifentanil and concurrent administration of glycopyrrolate on the cardiovascular response to intubation. †Significant difference between groups, $P < 0.01$ (ANOVA). *Significant within-group difference compared with before intubation ($P < 0\ 01$). HR = heart rate

	Before anaesthesia (t=0 min) Mean (SEM)		Before intubation (t=3 min) Mean (SEM)		After intubation (t=4 min) Mean (SEM)	
	MAP	HR	MAP	HR	MAP	HR
Remifentanil (n=10)	89 (2.2)	84 (5.2)	50 (2.3)	63 (4.0)	58 (3.4)*	63 (4.3)*
Saline (n=10)	89 (2.3)	78 (3.6)	78 (4.7)	84 (4.8)	118 (4.6)†	108 (4.4)†
Remifentanil and glycopyrrolate (n=10)	95 (4.6)	89 (5.4)	59 (2.2)	80 (4.0)	70 (5.5)*	88 (5.2)*
Glycopyrrolate (n=10)	94 (2.7)	81 (3.2)	73 (2.0)	87 (3.9)	115 (2.7)*†	110 (5.0)*†

Comparison of endogenous and recombinant human ORL-1 receptors expressed in SH-SY5Y and Chinese hamster ovary cells

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The endogenous agonist for the orphan opioid receptor ORL-1[1 2] has been identified as nociceptin or orphanin FQ.[3 4] ORL-1 receptors are coupled to adenylyl-cyclase, voltage-sensitive Ca^{2+} and K^{+} channels where nociceptin/orphanin FQ reduces cAMP formation, reduces Ca^{2+} influx and enhances an outward K^{+} conductance.[3-7] The recent introduction of $[^{125}I]Tyr^{14}$-nociceptin with high specific activity has enabled detailed radioligand binding studies of ORL-1 to be performed. In this study we present a comparison of the binding characteristics of $[^{125}I]Tyr^{14}$-nociceptin and adenylyl cyclase inhibition in Chinese hamster ovary (CHO) cells expressing the recombinant human ORL-1 receptor ($CHO_{ORL\text{-}1}$), with the same receptor endogenously expressed in SH-SY5Y cells.

$CHO_{ORL\text{-}1}$ cells were maintained in DMEM:F12 (50:50) containing 5% fetal calf serum, 2 mM glutamine, 200 μg ml^{-1} hygromycin B and 200 μg ml^{-1} G418. SH-SY5Y cells were maintained in minimum essential medium as previously described.[7] The binding of $[^{125}I]Tyr^{14}$-nociceptin was measured in membrane suspensions (1 ml) prepared from $CHO_{ORL\text{-}1}$ cells in Tris (50 mM), $MgCl_2$ (5 mM), BSA (0.5%) buffer at pH 7.4. Bound and free ligand were separated at equilibrium (30 min) by rapid vacuum filtration. cAMP was measured in whole-cell suspensions in Krebs/HEPES buffer containing BSA (0.5%) at pH 7.4, as previously described.[7] To prevent protease digestion of labelled and unlabelled nociceptin, binding and cAMP experiments were performed in the presence of amastatin, bestatin, captopril and phosphorhamidon (30 μM). The binding of $[^{125}I]Tyr^{14}$-nociceptin to SH-SY5Y and $CHO_{ORL\text{-}1}$ membranes was dose-dependent and saturable. Hill analysis of isotope dilution experiments yielded B_{max} and K_d values as shown in table 3. Nociceptin produced a dose-dependent inhibition of forskolin-stimulated cAMP formation in both cell types; pIC_{50} and I_{max} values are shown in table 3.

Table 3 Comparison of $[^{125}I]$-Tyr^{14}-nociceptin binding and cAMP inhibition in $CHO_{ORL\text{-}1}$ and SH-SY5Y cells. Data are mean (SEM). *Significantly different compared with SH-SY5Y cells

	SH-SY5Y	$CHO_{ORL\text{-}1}$
Binding		
pK_d (nM)	10.23 (0.19) (0.058)	9.87 (0.02) (0.133)
B_{max} (fmol/mg protein)	11.5 (4.7)	1122.0 (64.9)*
cAMP		
pIC_{50} (nM)	7.14 (0.14) (72.4)	10.34 (0.07) (0.045)*
I_{max} (%)	47.4 (5.8)	94.4 (2.2)*

These data confirm the negative coupling of the human ORL_1 receptor to adenylyl cyclase and the usefulness of $[^{125}I]Tyr^{14}$-nociceptin in studies of orphan receptor pharmacology. The differences in binding pK_d and functional pIC_{50} are under investigation.

Acknowledgments

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Effects of nociceptin on cAMP formation in rat cerebrocortical, cerebellar and brainstem membranes

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Nociceptin is the endogenous agonist of the orphan receptor ORL-1 that is found scattered throughout the central nervous system.[1 2] In cells expressing recombinant ORL-1 receptors nociceptin inhibits forskolin-stimulated cAMP formation with an IC_{50} in the nanomolar range.[1 2] In this study we have examined the effects of nociceptin on cAMP formation in membranes from rat cerebrocortex, cerebellum and brainstem to study regional differences in coupling of ORL-1.

Membranes from cerebrocortex, cerebellum and brainstem were prepared from Wistar rats (200–250 g) by homogenization and centrifugation.[3] The assay buffer was Tris (50 mM), $MgCl_2$ (3 mM), BSA (1%), ATP (0.5 mM), GTP (0.1 mM), phosphocreatine (20 mM), creatine phosphokinase (30 EU ml^{-1}), peptidase inhibitors (30 μM; captopril, amastatin, bestatin, phosphoramidon) and IBMX (0.5 mM), pH 7.4. Nociceptin was included at 10^{-11}–10^{-6}M. In some experiments nabilone (a cannabinoid agonist, 1 μM), SR141716A (a central cannabinoid antagonist, 1μM)[4] and forskolin (1 μM) were included. cAMP was measured using a radio receptor assay. Data are means (SEM) ($n \geq 4$).

Forskolin produced a 285(21)%, 234(11)% and 215(19)% stimulation of cAMP formation in rat cerebrocortical, cerebellar and brainstem membranes, respectively. In all membranes, nociceptin failed to inhibit basal and forskolin-stimulated cAMP formation up to 1 μM. As internal positive controls, nabilone inhibited basal cAMP formation in all membranes; the inhibition was reversed by SR141716A.

Nabilone inhibited basal cAMP formation through G_i protein, indicating that G_i protein is functional. In addition, forskolin increased cAMP formation by directly stimulating adenylyl cyclase. These data confirm the integrity of both G_i and adenylyl cyclase. Collectively these data suggest that ORL-1 receptors in rat brain may uncouple during membrane preparation, although further studies are required.

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First identification of nociceptin in human cerebrospinal fluid

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Nociceptin/orphanin FQ is the endogenous ligand for the orphan opioid receptor.[1 2] In animal studies analgesic,[3] hyperalgesic[1 2] and/or antiopioid[4] actions have been reported that may depend on the method and route of administration.[4 5] This study was designed to see if nociceptin could be detected in human cerebrospinal fluid (CSF) and plasma. In addition, we sought to compare two patient groups: one experiencing labour pain (Group 1) and a second group presenting for elective Caesarean section (Group 2).

Twenty patients were recruited, with 10 in each group. All participants gave written informed consent for inclusion in the study. In each group blood was taken at the time of siting an i.v. catheter and 0.2–0.5 ml of CSF was removed from the spinal needle before injection of intrathecal anaesthetic. Plasma and CSF samples were acidified with 1% trifluroacetic acid (v:v, TFA) and nociceptin extracted using a C18 SepPak cartridge with 0.1% TFA/60% acetonitrile as an eluant. Freeze-dried and reconstituted samples were assayed for nociceptin using a radioimmunossay kit (Phoenix Pharmaceuticals, CA, USA) with a minimum sensitivity of 0.5 pg/ml.

Group 1 patients had a mean age of 28 yr (range 25–29) and included five presenting for induction for postmaturity and one for pre-eclampsia. In group 1, five patients received pethidine but this did not appear to affect our results. Group 2 patients had a mean age of 31 yr (range 28–39) and none had coexisting medical problems. Nociceptin was identified in all CSF samples and 16/20 plasma samples (table 4). There were no differences between the groups for either plasma or CSF (plasma, $P = 0.119$; CSF, $P = 0.406$; Mann–Whitney *U* test) nociceptin concentrations.

We have identified nociceptin in both CSF and plasma of pregnant humans. Despite the early description of hyperalgesic actions of this peptide,[1 2] there was no association between nociceptin concentrations and an acute pain state. Further detailed clinical studies are required.

Table 4 Mean (SD) nociceptin concentrations. Group 1 = women experiencing labour pain; Group 2 = women presenting for elective Caesarean section; CSF = cerebrospinal fluid; *by Wilcoxon signed rank test

	Nociceptin (pg ml^{-1})		
Group	Plasma	CSF	*P* (plasma *vs* CSF)*
1	63.39 (33.26)	13.73 (23.79)	0.028
2	52.49 (34.25)	7.59 (21.58)	0.009

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Hazards of carbon dioxide insufflation during thoracoscopy

Editor,—I read with interest the review article on the anaesthetic implications of thoracoscopic sympathectomy.[1] When endobronchial anaesthesia is used, carbon dioxide may be insufflated only initially into the ipsilateral pleural space to augment lung collapse. In contrast, when a tracheal tube is used, carbon dioxide is insufflated continuously until the end of surgery. The report assumes that hypoxic pulmonary vasoconstriction (HPV) fails during one-lung ventilation achieved by endobronchial anaesthesia, while it remains intact after tracheal intubation, as the ipsilateral lung is only partially collapsed.[1] This assumption is based on previous reports showing that when more than 70% of the lung is atelectatic, compensation by HPV appears to be ineffective.[2] The authors prefer tracheal intubation during thoracoscopy to endobronchial anaesthesia because of its simplicity, decreased cost, and improved oxygenation. To minimize the risk of inadvertent tension pneumothorax secondary to the continuous insufflation of carbon dioxide during tracheal anaesthesia, a pressure-limited, variable flow of carbon dioxide is recommended.[1]

Experimental work in swine has shown that positive pressure insufflation during thoracoscopy results in significant haemodynamic compromise despite the use of selective lung ventilation: cardiac index, mean arterial pressure, and left ventricular stroke work index decreased, whereas pulmonary artery and central venous pressure increased at an insufflation pressure of 5 mm Hg or greater.[3] Thus, carbon dioxide insufflation into the closed chest cavity to a pressure as low as 5 mm Hg may create a physiological response very similar to that of a unilateral tension pneumothorax,[4] with a consequent haemodynamic instability secondary to decreased venous return and/or mediastinal shift.

Our anaesthetic technique during video-assisted thoracoscopy depends on double-lumen intubation which provides selective ventilation of the contralateral lung while allowing collapse of the ipsilateral lung without the need for carbon dioxide insufflation. Selective lung ventilation with 100% oxygen ensures adequate oxygenation throughout the procedure, as checked by continuous pulse oximetry. HPV is most active when 30–70% of the lung is hypoxic.[2] The original intrapulmonary shunt secondary to one-lung collapse is about 40–50%, and is decreased to 20–30% by active HPV,[5] as well as by gravity, and collapse of the non-ventilated lung. Partial collapse of the lung on the thoracoscoped side occurs when air enters the pleural cavity. To augment collapse, the lumen of the double-lumen tube on the thoracoscoped side is opened to room air, while suction is intermittently applied. Since we have used selective contralateral lung ventilation, and avoided carbon dioxide insufflation into the ipsilateral pleural space, we have encountered no serious haemodynamic complications secondary to inadvertent tension pneumothorax.

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Midazolam given as an intranasal spray in children

Editor,—We read with interest the article about the pharmacokinetics of midazolam given as an intranasal spray by Björkman, Rigemar and Idvall.[1] The authors described the intranasal application of midazolam spray as a practicable method with high bioavailability in adult surgical patients. As the authors noted, intranasal spray application of midazolam could also be useful in children because of the described pharmacokinetic and pharmacodynamic advantages.

In particular, ambulatory anaesthesia in children requires rapid and effective premedication. Midazolam is well known for its anxiolytic, euphoric, amnesic and sedative qualities. Although various routes of administration in children have been approved for this drug, none is without problems.

After rectal application of midazolam 0.5 mg kg^{-1}, an effect typically appears within 15 min. However, 20% of children refuse this approach.[2] Sublingual administration of midazolam produces a faster effect, but requires a flavour corrigent because of its bitter taste.[3] Even then, acceptance is poor; the liquid is often expectorated,[4] and many children reject a second application. Additionally, the incidence of postoperative nausea and vomiting is highest after oral midazolam.[2]

In the search for an alternative, it has been shown that nasal bolus administration of midazolam 0.2 mg kg^{-1} is an effective way to achieve rapid onset of sedation immediately before induction of anaesthesia in children.[5,6] A higher dosage of midazolam 0.3 mg kg^{-1} did not increase the effects.[6] Intranasal midazolam achieves good conditions for the induction of anaesthesia with a maximum effect attained 5–10 min sooner than with rectal or oral application. The euphoric effect is more potent, and the sedative component is less than with rectal midazolam.[7] The main disadvantage of intranasal midazolam administration is a burning discomfort in the nasal mucosa and—similar to oral application—a bitter taste when midazolam runs into the pharynx.[8] In all these articles, nasal midazolam was administered as a bolus dose.

Because of the reported side effects, we introduced undiluted midazolam (15 mg in 3 ml, Dormicum, Hoffmann-La Roche, Grenzach-Wyhlen, Germany) via a nasal spray. Our pump spray applicator (Calmar-Albert dispensing systems, Hemer, Germany), normally used for rhinorrhoea, produces a fine, equally distributed aerosol of midazolam. Each application delivers a standard 0.12 ml, which corresponds to midazolam 0.6 mg. A new application set is used for each patient. The glass bottles and aerosol applicators can be sterilized after use.

For 1 year, children in our outpatient department aged 1–10 years have received midazolam 0.2 mg kg^{-1} via pump spray for premedication. We noticed a rapid onset of mild sedation, and euphoria 5–10 min after administration, which allowed a calm separation of the child from the parent. For safety reasons, pulse oximetry was always used after nasal midazolam administration. However, we did not observe any impairment of vital functions, as has been reported by other authors.[1–4] In our preliminary observations, children tolerated the spray application much better than the bolus administration. We observed fewer complaints of bitter taste and mucosal irritation. This leads to better acceptance and enhances the child's and the parent's trust in the anaesthetic procedure. On the basis of our experience, we recommend this new form of nasal midazolam administration via nasal spray.

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Editor,—We thank Drs Thum, Heine, Hollenhorst and Leuwer for supporting our suggestion with some clinical data. It should be noted, that judging by our results, midazolam 0.2 mg kg^{-1} given by spray is a higher effective dose than 0.2 mg kg^{-1} given as drops or bolus. But a general recommendation to use midazolam by intranasal spray in small children should be based on a full report of the effect profile. We look forward to seeing these data published.

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The CardioPump: CEPOD guidelines and validation of new techniques

Editor,—Modern methods of cardiopulmonary resuscitation were introduced in 1960 after publication of the classic article by Kouwenhoven, Jude and Knickerbocker[1] on closed-chest cardiac massage. The CardioPump has been developed for resuscitation during cardiac arrest with the perceived advantage of increasing the forward flow of blood. We report a case in which the CardioPump was used, and a complication that may be associated with it and which was discovered only at postmortem examination.

A 60-year-old bricklayer with a basicervical fracture of the right hip underwent general anaesthesia for a right-sided AO dynamic hip screw. He was admitted to hospital 7 days before operation. Anaesthesia was induced with thiopentone 400-mg and fentanyl 75 µg. A 3 in 1 block was performed with 30 ml bupivacaine 0.375% using a nerve stimulator. The patient was subsequently given atracurium 50 mg and intubated with a size 9.0 oral tracheal tube. Anaesthesia was maintained with isoflurane in oxygen and nitrous oxide, using intermittent positive pressure ventilation. Following manipulation of the injured leg, desaturation from an SpO_2 of 96% to 90% was noted, together with a fall in end-tidal PCO_2. The patient developed a tachycardia that proceeded to a electromechanical dissociation (EMD) cardiac arrest. Cardiopulmonary resuscitation (CPR) was started using the European Resuscitation Council Guidelines for an EMD arrest.[2] The Ambu CardioPump was used to aid resuscitation attempts, which were continued for 45 min with no effect. Resuscitation was then abandoned. At postmortem, a pulmonary embolism was found to be the cause of the cardiac arrest. Other findings included a haemoperitoneum associated with a 4 × 4 cm tear in the mesentery of the small bowel adjacent to the third part of the duodenum. Associated with this was a small traumatic laceration on the superior surface of the liver, adjacent to the insertion of the falciform ligament. Three fractured ribs (four, five and six) on the left side of the chest consistent with attempted resuscitation were also noted.

The CardioPump device consists of a horizontal handle, a piston and a suction cup. The radius of the suction cup is 6.5 cm and the height of the device is 13.5 cm. The device is placed in the midsternal position and 80–100 compressions per minute are performed at a pressure of 30–50 kg (as marked on the pump), equivalent to a chest excursion of 3.8–5.1 cm in standard CPR. The decompression phase produces a negative pressure of approximately 10 kg. The compression and decompression phases are performed in a ratio of 1:1.[3]

Laceration of the liver and tearing of the mesentery of the small bowel adjacent to the third part of the duodenum can arise from standard CPR, especially if it is carried out incorrectly by the malpositioning of sternal compression. However, a new device was used in this case and its contribution to this complication is not known. The intra-abdominal trauma may be related to the higher pressures consistently produced in the compression phase with this device compared with standard CPR. We postulate an alternative theory. The active decompression phase may have contributed to the trauma as a considerable negative pressure is generated, and compared with standard CPR there is a greater change in intrathoracic and hence intra-abdominal pressure. We would also suggest that if this device were to be incorrectly positioned, that is below the sternal midpoint, the potential for intra-abdominal trauma would be increased.

The recent postgraduate resuscitation issue of the *British Journal of Anaesthesia* raises the question of the effectiveness of new resuscitation devices, asking if they are more beneficial than traditional CPR and if they carry added risks.[4] Only when these questions are answered can definitive recommendations be made about the use of such devices.

There is little information available about complications associated with active compression–decompression CPR. One of the many reasons for carrying out postmortem examinations is to monitor the effectiveness and side effects of new medical and surgical therapies. A joint recommendation from the Royal Colleges of Surgeons, Physicians and Pathologists published in 1991[5] stated that there should be an increase in hospital postmortem examinations, in part to gather information on new treatments. This point has been reiterated in the National Confidential Enquiry into Perioperative Deaths.[6] We feel that nonsurvivors of CPR using these new methods of resuscitation should undergo postmortem examination to look for complications before such techniques are accepted as standard practice.

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Submandibular duct stone and difficult tracheal intubation

Editor,—A 54-year-old male presented for extracorporeal shock wave lithotripsy. Apart from renal calculi he was in good health (weight 64 kg, height 166 cm, BMI 23.23). He had no symptoms relating to the mouth, tongue or saliva. He had received two uneventful general anaesthetics in the preceding 3 weeks, neither of which needed tracheal intubation. There was no abnormality detected on physical examination: oral examination revealed a Mallampati class II intubation score.

Anaesthesia was induced with propofol 150 mg, fentanyl 100 µg and atracurium 50 mg. His lungs were ventilated easily with oxygen 33%, nitrous oxide 66% and sevoflurane 2%. On laryngoscopy, 3 min later, the tongue was found to be slightly deviated to the left and only the tip of the epiglottis was visualized. Manual ventilation of the lungs was resumed. After two unsuccessful attempts at intubation had been made, a size 4 laryngeal mask airway (LMA) was inserted. Surgery proceeded uneventfully and the LMA was removed after reversal of the neuromuscular blocking drug. Detailed examination of the mouth revealed a swelling at the base of the tongue on the right side. Postoperatively, the patient was referred to an otorhinolaryngologist, who suspected submandibular gland swelling because of stone formation in the submandibular duct. Subsequently, sialolithiasis of the submandibular duct was confirmed by radiography. Two weeks later, the stone was removed under general anaesthesia; tracheal intubation was achieved using the McCoy laryngoscope and a gum elastic bougie.

Difficult laryngoscopy and intubation because of masses under the tongue such as a lingual thyroid,[1] sialadenitis[2] or sublingual haematoma[3] have been reported. Swelling of the tongue following general anaesthesia can also occur in association with angioedema.[4] It is unlikely that the swelling under the tongue in this patient was related to the recent episodes of general anaesthesia; both were atraumatic and neither required intubation. There was no evidence of sialadenitis or sublingual haematoma and angioedema usually causes generalized swelling of the tongue that becomes apparent within a few hours.[4,5]

This case serves as a reminder that the anaesthetist should always make a thorough preoperative intra-oral inspection, especially where preoperative Mallampati is not class I.

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Treatment of postoperative nausea and vomiting by acupressure

Editor,—The letter from Drs Harper and Barker[1] on post-operative nausea and vomiting poses the question, "Are there non-drug interventions that can help, such as reducing the length of the preoperative fast or the use of intra-operative fluids?"

A non-drug intervention that appears to have been overlooked is the use of acupressure by applying a stud on elasticated bands to the P6 (Neiguan) point on the wrists. Several studies have indicated that this inexpensive measure can reduce the incidence of postoperative nausea and vomiting[2] and also be of benefit in morning sickness[3] and chemotherapy-induced sickness.[4]

Harper and Barker conclude by making a plea for more co-ordinated research to provide some answers. In view of the promising results already obtained, it would appear that P6 acupressure is worthy of further research. A study is in progress at my own hospital investigating this method as a means of reducing the incidence of nausea and vomiting associated with patient-controlled analgesia.

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Editor,—We thank Dr Chow for his interest in our letter. We would support any research into means of reducing postoperative nausea and vomiting (PONV) to a minimum. However, acupressure, like other single-agent regimens investigated, has been only partially effective in reducing the incidence of PONV. We would still feel that future research should be directed at treating those patients at risk of PONV, as ascertained by a scoring system, with one, two or three combined active treatments. This could be one or two antiemetic agents with different sites of action plus non-drug intervention such as acupressure or intraoperative fluids. Perhaps in this way, the incidence of PONV can be reduced to minimal levels.

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Local analgesia in early and late stages of labour

Editor,—As an obstetrician, I read with interest the article by Capogna and colleagues.[1] The authors measured the minimum local analgesic concentration (MLAC) of bupivacaine in both the early and late stages of labour. They conclude that advancing labour requires an increased concentration of extradural bupivacaine for pain relief. Regional anaesthesia has a direct influence over obstetric practice in terms of operative delivery and progress of labour, and research into optimal intrapartum analgesia is always of interest. Research like this is lacking.[2]

From an obstetric point of view, there are several factors of which anaesthetists should be aware when considering this study. Although the two groups were well matched with respect to maternal characteristics, it would have been helpful to have had more intrapartum details. Labours induced with prostaglandins are longer than spontaneous labours, and an induction of labour with prostaglandins or oxytocin can cause uterine activity in the absence of progressive cervical dilatation. Were inductions of labour included in this sample? We are told that 20 out of 30 women had oxytocin. Was the oxytocin given before the visual analogue profile scores (VAPS)? It would be wise to consider these women as a separate group, as the use of oxytocin suggests that labour was prolonged because of incoordinate uterine activity, cephalopelvic disproportion or induction. Either way, labours with oxytocin are abnormal and should be considered separately from spontaneous labours, which on average will be shorter in duration and hence have different, possibly lower, VAPS.

Finally, I disagree with combining data from nulliparous and multiparous women, as these two groups have very different intrapartum profiles. Nulliparous women are prone to incoordinate uterine activity at any stage of labour and require oxytocin to correct this. As a result labour can be longer. This is rarely the case with multiparous women.

Cervical dilatation is only one of many important intrapartum findings used to assess the stage of labour. Not only the degree of cervical dilatation, but also the *rate* of dilatation and foetal head descent should be considered, together with the women's parity, the quality and frequency of the uterine contractions and the size of the foetus.

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Editor,—We thank Dr Nunns for his comments on our study. We are aware of the differences between spontaneous and induced labours and therefore excluded induced labours from our sample. In some cases, oxytocin was given to the mothers, always after extradural analgesia, according to the obstetrician's wishes. However, the number of women who received oxytocin was not statistically different between the two groups.

I agree with the observation concerning the different intrapartum profiles of nulliparous and multiparous women. These two groups represent different 'species' of parturient, and I believe any study that seeks to minimize independent variables should exclude one or other group. In addition, all studies in obstetric anaesthesia should compare women at the same stage of labour.

However, in this study we did not evaluate the effect of MLAC on the duration or outcome of labour, but only the efficacy of the solution tested for a definite period (our study protocol observed analgesic efficacy for a maximum of 1 h). For this reason, we decided that a mixed group of nulliparous and multiparous women was acceptable

In the study, we showed that the MLAC of bupivacaine increased with advancing labour. That means that, when low concentrations of local anaesthetic are used, the first dose of local anaesthetic may need to be increased if labour has already advanced.

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A guide for tube exchange using a fibrescope and the plastic sheath of a guidewire in small children

Editor,—When managing a difficult airway, occasionally there is a need to replace a tracheal tube. For example, one may have to change a tracheal tube for a larger one after intubation through a laryngeal mask airway (LMA).[1 2] But, in small children, tube exchange techniques are not readily available.

As a guide for tracheal tube exchange, we used the plastic sheath of a guidewire within a central venous line set (B. Brown Medical, Bethlehem, PA). The sheath is a hollow plastic tube and has an internal diameter of about 3 mm and is about 65 cm long. It is supplied in a circular form (fig. 1A) and can be uncoiled in a half-circle shape (fig. 1B, C) because of its plastic character One may use any kind of plastic sheath that is a little malleable, has sufficient length, an inner diameter large enough to accommodate a fibrescope, and an outer diameter small enough to pass through a tracheal tube. The length of the sheath should be adjusted to only a few cm shorter than the working length of a fibrescope (the length of an Olympus LF-P is 60 cm). The square-cut leading edge of the sheath may be blocked half way on the curved inner surface of the tracheal tube, so we suggest making a bevel of about 45° on the convex side of its tip. The length of the tracheal tube to be changed should be pre-marked on the shaft of the sheath.

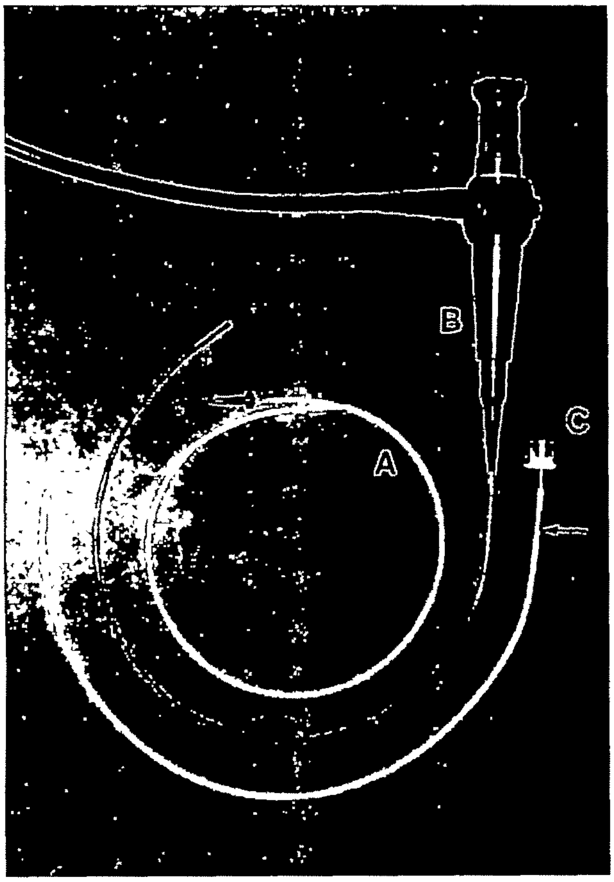

Figure 1 (A) a guidewire and sheath in an original form, supplied as a central venous line set (B. Brown Medical, Bethlehem, PA). (B) The modified guidewire sheath, shortened about 6 cm, through which a fibrescope (Olympus LF-P) is inserted. (C) The guidewire sheath is wedged into the distal end (arrow) of the shaft of a tracheal tube of 3.5 mm internal diameter cut at the middle.

We have exchanged a tracheal tube for a larger one after intubation through an LMA in two small children. One was a 4-year-old, 16-kg boy with Treacher–Collins syndrome, in whom a tracheal tube of 4.5 mm internal diameter was exchanged for a 5 5 mm tube. The other was a 5-year-old, 7.7-kg boy with Goldenhar's syndrome, in whom a 4 mm tracheal tube was exchanged for a 4.5 mm tube. To prevent potential mucosal damage from the sharp tip of the sheath, we inserted an ultrathin fibrescope (Olympus LF-P, outer diameter 2.2 mm) through the sheath beforehand (fig. 1B). We advanced the fibrescope into the trachea ahead of the sheath, with its proximal end abutting the fibrescope handle. We maintained the fibrescope *in situ* to confirm its intratracheal location while removing the tracheal tube and LMA from the mouth. While holding the sheath, we removed the fibrescope, off-loaded the tracheal tube and LMA, reloaded a larger tracheal tube over the sheath, reinserted the fibrescope into the sheath, and finally railroaded the larger one over the sheath to the desired depth. This method may prevent inadvertent extubation by continuously confirming the intratracheal location during the critical period of removing or inserting a tracheal tube over a tube exchanger, and can simultaneously adjust its depth Similar techniques have been reported,[3 4] but these were used in adults An alternative technique is also available· one can cut away the former tracheal tube as described by Gatell and colleagues [5] Then it is not necessary to pull out the fibrescope during removal of the first-tracheal tube, but one would have to load a new tracheal tube before the exchange. Additionally, the presence of a sheath can protect the expensive fibrescope from damage by a pair of scissors or scalpel

The presence of a fibrescope within the sheath can stabilize and strengthen it and may reduce potential mucosal injury by minimizing contact of the tip with tracheal mucosa Additionally, use of a fibrescope can prevent tracheobronchial rupture, which has been reported with the blind use of a tube exchanger.[6]

The sheath can be used only for 4.0 mm tracheal tubes or larger It also can be connected to an oxygen source or to a capnograph through an appropriate adaptor. For example, a 15 mm connector for a 2 0 mm tracheal tube can fit snugly into the sheath, or it may be wedged into the distal end of a 3.5 mm tracheal tube cut at the shaft (fig. 1C).

It is preferable if a tube exchanger, which can accommodate a fibrescope and has a blunt tip, is made of clear material to allow surrounding tissues to be seen. Additionally, if it has an inflatable balloon at the tip, just like a cuffed tracheal tube, it may reduce mucosal injury and anchor the tube exchanger at the subglottic area while the tube is being exchanged in young children.

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Sevoflurane for difficult tracheal intubation

Editor,—We read with interest the report and subsequent correspondence on the use of sevoflurane in patients with difficult airways.[1–3] These reports describe the use of a stepwise inhalation induction technique. While the use of such a cautious approach would seem prudent in patients with anticipated airway problems, the evidence suggests that this technique is associated with a higher incidence of complications.[4] A stepwise increase of inspired sevoflurane concentration is not only slower but also prolongs the second stage, resulting in an unacceptably high level of excitement and coughing. We would suggest that the technique of choice in patients with a difficult airway is to breathe sevoflurane 8% from the start, as this has a lower incidence of cough and excitement (2% and 10% respectively)[5] compared with a stepwise technique (12% and 31% respectively).[4] Apnoea is relatively uncommon with this technique (16%) and typically short-lived, the average time from loss of consciousness until resumption of spontaneous breathing being 10 s.[5] As the addition of nitrous oxide has little effect on the speed or quality of inhalation induction with sevoflurane,[6] we would recommend that in patients with difficult airways, sevoflurane is administered in oxygen 100%.

Sevoflurane alone can be used to facilitate tracheal intubation. We have found intubation conditions to be satisfactory at about 4 min in unpremedicated adults and at about 2.5 min in children. An alternative approach to facilitate tracheal intubation after a sevoflurane induction is to give a neuromuscular blocking agent once the vocal cords have been clearly visualized.

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1. Mostafa SM, Atherton AMJ. Sevoflurane for difficult tracheal intubation. *British Journal of Anaesthesia* 1997; 79. 392–393.
2. Board P. Sevoflurane in acute airway obstruction (letter). *British Journal of Anaesthesia* 1998; 80: 272–273.
3. Ip-Yam PC. Sevoflurane in acute airway obstruction (letter). *British Journal of Anaesthesia* 1998; 80: 273.
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Editor,—The authors refer to two papers[1,2] which, they suggest, recommend sevoflurane 8% in oxygen as the technique of choice in patients with a difficult airway.

Yurino and Kimura[1] report a 31.25% incidence of movements during inhalational induction with stepwise increments of sevoflurane 0.5% every third to fourth breath, compared with an incidence of 6.25% in a vital capacity induction of sevoflurane 4.5% in nitrous oxide–oxygen. The incidence of coughing was 6.25% in the vital capacity induction compared with 12.5% in the stepwise technique, but I would suggest that their stepwise technique is in no way comparable to the one described by Mostafa and Atherton, and myself.[3,4] The technique described in my report involves more rapid increments of at least 1% or more after pre-oxygenation, depending on the maintenance of spontaneous ventilation and control of the airway. It is worth noting that the original authors describe the coughing and movements as being of mild intensity.[1]

Thwaites, Edmends and Smith[2] compared inhalational induction using sevoflurane 8% in nitrous oxide–oxygen to i.v. propofol ($n = 102$), and reported purposeful movement in three patients in the propofol group compared with five in the sevoflurane group. Although the incidence of coughing was only 2% during inhalational induction, the same authors also reported an 8% incidence of coughing during the transition from induction to maintenance of anaesthesia.

I have not found coughing and excitement to be a major problem in an ongoing audit of a predominantly Asian group of patients with head and neck tumours. A 16% incidence of apnoea in the use of a sevoflurane 8% induction cannot be ignored.[2] Indeed, in one patient with tonsillar carcinoma who underwent sevoflurane 8% vital capacity induction in our hospital, the duration of apnoea would have led to hypoxia if assisted ventilation had been impossible. Although the use of sevoflurane 8% results in faster onset of anaesthesia, the advantage of gas induction is not speed but safety.[5] A stepwise induction enables the experienced anaesthetist to assess airway patency and the ability to assist ventilation. The low blood-gas solubility of the agent allows the option to abort before an unnecessarily deep plane of anaesthesia is reached.

In conclusion, before inhalational induction with sevoflurane 8% can be favoured over a stepwise technique, the outcome from the management of actually difficult cases needs to be reported.

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1. Yurino M, Kimura H. Induction of anaesthesia with sevoflurane, nitrous oxide and oxygen: A comparison of spontaneous ventilation and vital capacity rapid inhalation induction (VCRII) techniques. *Anaesthesia and Analgesia* 1993; 76: 598–601.
2. Thwaites A, Edmends S, Smith I. Inhalational induction with sevoflurane: a double-blind comparison with propofol. *British Journal of Anaesthesia* 1997; 78: 356–361.
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4. Ip-Yam PC. Sevoflurane in acute airway obstruction (letter). *British Journal of Anaesthesia* 1998; 80: 273.
5. Mostafa SM, Atherton AMT. Sevoflurane in acute airway obstruction (letter). *British Journal of Anaesthesia* 1998; 80: 273.

Editor,—The figures quoted for cough and excitement with a high-dose technique of inhalation induction with sevoflurane are 2% and 10% respectively.[1] However, other research has reported complication rates of 25% for coughing[2] and 38% for excitement[3] when using sevoflurane 8% from the outset. These are higher than the quoted rates for a stepwise approach (12% and 31% respectively).[4,5] Complication rates seem to be lower if a vital capacity technique is used, but such a technique would not be easy to use in someone with a difficult airway.

Coughing may also be linked to how quickly a concentration of sevoflurane 8% is reached.[1] The theory is that if the anaesthetic circuit is pre-primed with sevoflurane 8%, this leads to an abrupt increase in inspired vapour concentration when the facemask is applied. This is irritant and leads to coughing. The alternative — pre-oxygenating the patient and then adding the sevoflurane 8% to the flow — allows dilution of the agent and a more gradual increase in inspired vapour concentration. This is better tolerated by the patient (and is more akin to the stepwise approach).

More serious complications, such as laryngospasm, have been reported in patients in whom anaesthesia was induced with sevoflurane 8%.[6] Severe hypoventilation has also been noted to occur in children.[6] There are several reports of profound bradycardia in children during induction of anaesthesia with sevoflurane using the high-concentration approach.[7] These are reasons for adopting a more cautious approach, especially with a difficult airway.

Finally, 29% of patients in whom anaesthesia was induced with sevoflurane recalled an unpleasant smell afterwards.[1] Half of these described the whole induction experience as unpleasant, compared with none in a propofol control group. Patient comfort is surely the most compelling reason for an incremental approach; the stepwise approach allows patients to become familiar with the smell in a gradual, controlled manner rather than being suddenly exposed to the full pungency of the vapour. They remain calm and confident in their anaesthetist. There is still rapid loss of consciousness, because of the low blood gas solubility coefficient of sevoflurane, following which rapid progression to maximum concentration minimizes the excitement phase.

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2. Yurino M, Kimura H. A comparison of vital capacity breath and tidal breathing techniques for induction of anaesthesia with high sevoflurane concentrations in nitrous oxide and oxygen. *Anaesthesia* 1995; 50: 308–311.
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4. Yurino M, Kimura H. Induction of anaesthesia with sevoflurane, nitrous oxide and oxygen: A comparison of spontaneous ventilation and vital capacity rapid inhalation induction

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Early *vs* late tracheal extubation after CABG surgery

Editor,—The recent paper by Berry and colleagues highlights the important issue of the safety of early tracheal extubation after coronary artery bypass graft (CABG) surgery.[1] A crucial question is whether the potentially adverse effects of tracheal extubation on myocardial oxygen balance are significant when the heart is recovering from the ischaemic insult associated with proximal aortic crossclamping. Early extubation after CABG surgery is safe only if it does not exacerbate perioperative cardiac muscle injury.

The regulatory cardiac contractile protein, cardiac troponin I (cTnI), is present exclusively in cardiac muscle tissue and is an accurate biochemical marker of perioperative cardiac muscle injury.[2–5] In a recent study comparing Holter continuous ECG ST segment analysis with serum cTnI concentrations during the postoperative period after CABG surgery, we found that early postoperative electrocardiographic myocardial ischaemia was associated with elevated postoperative serum cTnI concentrations.[6] Data from three out of 30 patients in this study indicated that electrocardiographic myocardial ischaemia within the first 8 h after the end of cardiopulmonary bypass was precipitated or exacerbated by withdrawing sedation in preparation for tracheal extubation. Although for these three patients the electrocardiographic myocardial ischaemia was immediately resolved by resedation and mechanical ventilation, postoperative serum cTnI concentrations were elevated. Data from the study by Berry and colleagues[1] show that a small but significant proportion of patients (10%) who meet standard early extubation criteria have a high myocardial ischaemic burden (>15 min h^{-1}) during the early postoperative period. As the incidence of myocardial ischaemia falls exponentially with time during the early postoperative period,[7] the earlier that extubation is performed, the greater is the chance that it will occur simultaneously with electrocardiographic myocardial ischaemia.

Therefore for patients who fulfil the criteria for early extubation after CABG surgery, during weaning from postoperative sedation, the continuous ECG ST segment monitor (now incorporated into most ICU or operating theatre monitors) should be closely observed. If myocardial ischaemia is present, extubation should be postponed until these ECG ST segment abnormalities have been resolved. Although in the study by Berry and colleagues[1] 19 out of 359 episodes of electrocardiographic myocardial ischaemia occurred during the extubation period, it is not clear first, in how many patients this occurred or second, whether extubation precipitated or exacerbated myocardial ischaemia.

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1. Berry PD, Thomas SD, Mahon SP, Jackson M, Fox MA, Fabri B, Weir WI, Russell GN. Myocardial ischaemia after coronary artery bypass grafting: early *vs* late extubation. *British Journal of Anaesthesia* 1998; **80:** 20–25.
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Editor,—Thank you for the opportunity to reply to the comments of Dr Tupper-Carey. As he suggests, it is important to assess the impact of any adverse haemodynamic changes associated with early extubation on the total ischaemic load experienced If the "extubation period" is defined as 30 min either side of tracheal tube removal, then in our study, six patients in the early extubation group and two in the late extubation group experienced ischaemic episodes in this period. It is clear from previous studies that the incidence of electrocardiographic ischaemia is greatest in the 8 h after surgery and declines with time. Our early extubation group were allowed to waken as soon as they returned from the operating theatre and the average time of extubation was almost 11 h earlier than in the late group. Nevertheless, we found no difference in the total incidence or severity of postoperative ischaemia. Review of our haemodynamic data demonstrated that the major haemodynamic changes occur within the first 30 min after discontinuing volatile anaesthetics, and the haemodynamic effects of extubation are mild and shortlived. Extubation itself did not appear to initiate or exacerbate ECG ischaemia.

Dr Tupper-Carey has observed that patients with early postoperative ST-segment change have elevated levels of troponin I. Troponin I is cardiospecific and peak levels are seen 1 day after the onset of myocardial necrosis, but elevated levels persist for 3–4 days. Patients undergoing aortic crossclamping may suffer significant degrees of myocardial ischaemia and necrosis despite all attempts at cardioprotection. This intraoperative myocardial insult may lead to both troponin I release and postoperative myocardial ECG ischaemia in those patients suffering the severest insult.

We do not dispute the importance of these changes. However, it is clear from our study that the postoperative management strategy of early extubation does not influence their frequency or severity.

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1. Mair J. Cardiac troponin I and troponin T: are enzymes still relevant as cardiac markers? *Clinica Chimica Acta* 1997; **257:** 99–115.

Venous air embolism and PEEP: a clinical research blind-spot

Editor,—The recent clinical study by Giebler and colleagues on 89 patients undergoing neurosurgery in the sitting position reported that the use of 10 cm H_2O positive end-expiratory pressure (PEEP) did not reduce their overall 26% incidence of venous air embolism (VAE).[1]

While not necessarily disagreeing with their conclusion that the use of PEEP "cannot be recommended", I believe they misinterpreted one of the findings of Meyer and colleagues,[2] who reported a zero incidence of VAE in 30 children being managed with PEEP and a MAST suit, compared with a 26% incidence in a control group. Though the "filling pressures" in both the Meyer and the Giebler studies "did not differ", it should be noted that, in the Meyer study, the reported right atrial pressures would have been sufficient to distend the venous system of many of the sitting children to a level approximating the level of the jugular bulb. The protective mechanism of a MAST suit and PEEP could not be translated to adult patients, as it is not clinically feasible to maintain the venous pressure at equivalent high levels.[3]

Although maintaining an elevated venous pressure will not prevent VAE in adult patients, it will in theory serve to promote the temporary collection of embolized air in the superior vena cava and even the internal jugular veins,[4 5] and to reduce the risk of a massive life-threatening embolism.[4] I believe that greater emphasis should be placed on the need to maintain a raised central venous pressure, whether it be by MAST suit application, transfusion or a combination of these.

In our hospital, neurosurgery with the patient in the sitting position has not been performed for many years. For clarification of several issues, therefore, I seek advice from centres where such surgery is performed. Does maintaining the central venous pressure at, for example, 10 mm Hg using a transducer zeroed at the level of the upper part of the right atrium, result in embolized air collecting or 'pooling' upwards in the superior vena cava, either temporarily or in part, as it does in a model[3] and in sheep?[4 5] Second, does the entry of even small volumes of air create in humans, as it does in sheep, a readily identifiable pressure differential between two different levels in the vertically positioned superior vena cava, so allowing a diagnosis of VAE earlier than, or at the same time as, it is identified by Doppler?[5]

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1. Giebler R, Kollenberg B, Pohlen G, Peters J. Effect of positive end-expiratory pressure on the incidence of venous air embolism and on the cardiovascular response to the sitting position during neurosurgery. *British Journal of Anaesthesia* 1998; **80**: 30–35.
2. Meyer P-G, Cuttaree H, Charron B, Jarreau M-M, Perie A-C, Sainte-Rose C. Prevention of venous air embolism in paediatric neurosurgical procedures performed in the sitting position by combined use of MAST suit and PEEP. *British Journal of Anaesthesia* 1994; **73**: 795–800.
3. Pfitzner J. Prevention of venous air embolism: are humans like sheep ? *British Journal of Anaesthesia* 1995; **74**: 722–733.
4. Pfitzner J, McLean AG. Venous air embolism and active lung inflation at high and low CVP: a study in 'upright' anesthetised sheep. *Anesthesia and Analgesia* 1987; **66**: 1127–1134.
5. Pfitzner J, McLean AG, Crawshaw KM. Embolised air collection in the superior vena cava of 'upright' sheep. *Anesthesia and Analgesia* 1987; **66**:1135–1140.

Editor,—We appreciate Dr Pfitzner's letter in response to our article[1] and the interest in our clinical research. Dr Pfitzner feels that we may have misinterpreted the findings of Meyer and colleagues who reported a zero incidence of venous air embolism (VAE) in children managed with both PEEP and a MAST suit, compared with a 26% incidence in a control group.[2] Obviously, the distance between the right heart and jugular bulb or brain surface is much smaller in young children than in adults. As Meyer and colleagues reported an average central venous pressure of 11 mm Hg in children in the sitting position, this pressure may have been sufficient to minimize air entry and clinically relevant VAE in children, but is unlikely to be sufficiently high in adults, as indicated by the results of our study.[1] Accordingly, children are like neither adults nor sheep.

We rarely use anti-gravity suits, because the increase in filling pressures has been reported as only transient.[3] We care for many adults with heart disease and try to minimize cardiac volume overload during surgery. Whether PEEP at levels markedly in excess of 10 cm H_2O may be effective in decreasing the incidence of VAE and yet not impair cardiovascular performance is beyond the scope of our investigation. This is unlikely, however, as although PEEP increases venous pressure relative to atmosphere, it also decreases cardiac transmural filling pressures and thus cardiac filling and output.[4]

Whether an increased venous pressure will, in theory, serve to promote the temporary collection of embolized air in the superior vena cava and even in the internal jugular veins, as speculated by Pfitzner and colleagues,[5 6] and reduce the risk of massive life-threatening embolism, is certainly interesting. To our knowledge, clinical data on this topic are not available. However, Pfitzner[5] himself could not demonstrate clear evidence that blood volume or PEEP influenced the yield of air at aspiration.

Furthermore, from a clinical viewpoint, this hypothesis can hardly be tested in a quantitative fashion because a Doppler probe is placed over the heart but the superior vena cava cannot reliably be visualized by transoesophageal echocardiography. Accordingly, data collection from sitting sheep may be the only way to address Dr Pfitzner's hypothesis, but may be of questionable clinical relevance!

Therefore, we cannot provide an answer to Dr Pfitzner's question, as to whether a certain central venous pressure results in "trapping" of embolized air in the superior vena cava or, of even greater interest, in a step pressure gradient along the superior vena cava in the vertical position, allowing a potential diagnosis of VAE. The answer to this question may also depend on the presence and competence of venous valves in the jugular venous system, which in certain individuals may or may not be functional.[7] Indeed, differences in the venous valve system may benefit sheep but not human adults during VAE.

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1. Giebler R, Kollenberg B, Pohlen G, Peters J. Impact of positive end-expiratory pressure on the incidence of venous air embolism and on the cardiovascular response to attaining the sitting position during neurosurgery. *British Journal of Anaesthesia* 1998; **80**: 30–35.
2. Meyer PG, Cuttaree H, Charron B, Jarreau MM, Perie AC, Sainte-Rose C. Prevention of venous air embolism in paediatric neurosurgical procedures performed in the sitting position by combined use of MAST suit and PEEP. *British Journal of Anaesthesia* 1994; **73**: 795–800.
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Walking extradurals

Editor—Thank you for the opportunity to reply to the letter published in the May issue of the *British Journal of Anaesthesia*.[1] We are sorry that our title and editorial confused the authors. The inverted commas around "walking extradural" were meant to convey the fact that although such a regional blockade is commonly called an epidural it often involves a spinal component.

The use of combined spinal epidural analgesia in labour is controversial. Several authors from various centres including one from Queen Charlotte's Hospital itself[2] have questioned its routine use in labour.

Our editorial attempted to explore the possibility of ambulation in labour, its safety, the techniques available and possible effects on the mode of delivery. Few studies involving low dose regional blockade in labour have described accurately either the ability to walk or actual rates of ambulation. Low rates of ambulation and the use of higher concentrations of local anaesthetic solution in late labour may explain the inability of some studies to demonstrate any difference in obstetric outcome. We accept that the lower the total dose of local anaesthetic administered into the epidural space, the lower will be the resultant motor blockade. A small dose of local anaesthetic administered intrathecally with combined spinal epidural analgesia in labour has a very rapid onset for the anatomical reasons given. However, there is little evidence that this influences dose requirement and subsequent motor block several hours after the initial dose.

We accept that the combined spinal-extradural technique is popular and useful but we hoped that our editorial gave a balanced, cautious assessment of its potential in obstetrics.

We discussed the first use of the epidural catheter after a combined spinal-extradural. In this situation, the first dose is the test dose and should be given by someone able to identify and treat the consequences of intravenous and intrathecal placement of the catheter. Our use of the term "appropriately trained person" was intentional and not a substitution of the word "anaesthetist". It is entirely possible that a midwife could be trained to give this first dose provided that he or she is also trained to recognise the consequences of inadvertent intrathecal administration and that an anaesthetist is immediately available. The first dose should not be given by a patient-controlled epidural analgesia device in the absence of an appropriately qualified individual.

We did not advocate the use of a test dose of high concentration lignocaine or bupivacaine. Indeed, in our discussion on proprioception, we suggested that this was undesirable. We do not recommend flushing the epidural catheter immediately after placing it in the epidural space.

We did not say there was an excess incidence of meningitis after combined spinal-extradural but stated that an excess would limit the use of this technique. Penetrating the dura represents an even greater compromise of host defences than merely penetrating the ligamentum flavum. We do believe it is important to pay scrupulous attention to aseptic technique and the avoidance of chemical contamination when giving intrathecal drugs.[3] We accept that the use of the phrase "provides evidence for the inherent safety of the technique" was open to misinterpretation.

We wholeheartedly agree that the provision of safe, efficacious analgesia in labour should be a health care priority. We believe in a woman-centred approach based on informed choices of analgesia.

Further work is necessary to establish the benefits of ambulation in labour and to justify the routine use of additional interventions such as dural puncture; recently, disadvantages of subarachnoid opioid analgesia such as delayed gastric emptying[4] and an association with transient uterine hypertonus and resultant fetal distress, have been reported.[5,6]

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Change of nasogastric tube via Seldinger technique

Editor,—A14-year-old patient was admitted to our intensive care unit with multiple facial fractures and a head injury. During surgical repair of the fractures, a tracheostomy was performed and dental wiring completed. An x-ray after operation revealed a distended stomach and kinked nasogastric tube. The dental wiring made it impossible to open the patient's mouth. The kinked nasogastric tube was gently withdrawn in an attempt to straighten it. This was unsuccessful. The CT scan was examined and the faciomaxillary surgeon consulted about the integrity of the patient's nasopharynx and base of skull. Both appeared intact.

A standard Olympus LF-1 4.5 mm fibre-optic bronchoscope was used to enter the patient's stomach, and a soft J-tipped wire (145 cm, 0.032 inch diameter; code TSCF 32 146-3, Cook Group, Bloomington, USA) was passed into the stomach via the suction part of the bronchoscope. The wire was obtained from the urology theatres Once the wire was *in situ* the bronchoscope was withdrawn, and the nasogastric tube fed over the wire.

The procedure took 15 min and can be recommended as a safe and simple method of placing a nasogastric tube in a difficult patient.

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Observation and purpose: are ventilatory periodicities fine tuning or accidents of physiology?

Editor,—The recent paper from Galletly and Larsens[1] reports an extension of their previous work, in which they provided an explanation for one type of ventilatory periodicity[2,3]: cardioventilatory coupling. This causes the breathing rate to be entrained by the cardiac cycle: each breath tends to last a whole number of cardiac cycles and, in effect, the start of inspiration waits for the next cardiac cycle to begin. Their explanation was particularly welcome for being so simple, unlike some of the previous suggestions.[4] It is also welcome for acknowledging a 70-year-old observation by Coleman,[5] of which I, probably like many others with a respiratory interest, was completely unaware.

I am less at ease with the subtext running through their papers. In their most recent introduction[1] they write: "Although the physiological role of [cardioventilatory coupling] is not known...", implying that it does serve some physiological function, and they go on to speculate what this might be. At the end of their first paper,[2] they wrote that the relevance of coupling was unknown, but that it had implications for the interpretation of studies of heart rate variability and for understanding the genesis of breathing pattern. That is undeniable: it happens, and therefore it has consequences, whether or not these consequences are important. It is a different matter to talk about coupling having a role. Even if coupling has consequences, it does not mean that those consequences are the purpose of coupling.

In their latest study,[1] on the relation between respiratory sinus arrhythmia and cardioventilatory coupling, Galletly and Larsen suggest that these mechanisms are important (that is, by implication, they have a purpose) in reducing the effect of sleep or posture on pulmonary gas exchange. They also suggest that their finding of a link between the two phenomena strengthens the argument for a physiological purpose.

I suggest that a link between respiratory sinus arrhythmia and cardioventilatory coupling is entirely to be expected, if not inevitable, given that both depend on the interaction between the same two rhythmic processes. While it is possible that either or both phenomena are physiological adaptive mechanisms, they might just as easily be an accident of the closeness with which respiratory and cardiovascular control are interdependent. If coupling confers some advantage, what sort of evolutionary pressure is supposed to have brought it about? Cardioventilatory coupling is seen in humans only when at rest. Disorders of gas exchange in sleep are irrelevant in healthy subjects, and unlikely to have exerted evolutionary pressure.

I admit that evolutionary supposition is only supposition, and I have no evidence that respiratory sinus arrhythmia and cardioventilatory coupling are just an accident. It is difficult to think how supportive evidence could be gathered, which makes my suggestion of an accident a speculation rather than a hypothesis. Nonetheless, there is a lesson that carries over to the whole of research: beware of ascribing meaning to observation. In anaesthesia, we do not have to go far to find a similar mystery· why is there butyrylcholinesterase in our plasma? More generally, why do men go bald? Much of our physiology is without explanation, and possibly without purpose. Just because something is interesting — as cardioventilatory coupling is — does not mean that it has a purpose, although it can give useful insights into the way our physiology works. There is nothing wrong with continuing to make observations on coupling, but I should prefer to read in introductions, "It is not known if coupling has any physiological role .." rather than "Although the physiological role is unknown .."

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Editor,—During anaesthesia, the reflex coupling of inspiratory onset to the cardiac cycle is an important determinant of ventilatory timing.[1] In a recent paper, we examined the relationship that exists between respiratory sinus arrhythmia (RSA) and cardioventilatory coupling (CVC).[2] We observed that, during CVC, heart beats are generally placed at positions of the ventilatory cycle where they are maximally affected by RSA. This observation was unexpected and not, as Dr Goodman suggests, "inevitable". As experimental evidence has demonstrated that the presence of RSA may be important in optimizing pulmonary gas exchange,[3] we put forward a hypothesis that CVC, by maximising RSA, might also help pulmonary oxygenation. Because CVC occurs primarily during low arousal states, we suggested that coupling may aid gas exchange during sleep. In our paper we clearly stated "Whether the relationship between RSA and phase coupling is simply fortuitous...or the result of evolutionary design is open to question." We did not assume that coupling had a physiological role, only that a benefit may exist and warrants investigation.

Our conjecture of coupling optimizing cardiopulmonary function is a testable or falsifiable hypothesis. This is in contrast to the classification of coupling simply as an accident of evolution as Goodman proposes. To categorize any physiological process as an accident, simply because one cannot see what evolutionary pressure produced it, does little to advance our understanding of physiology. The case of butyrylcholinesterase is interesting. We cannot understand why the drug-metabolizing enzyme should be present, but that does not mean that it is without function. The "accident" may simply represent the anaesthetist's blinkered view of a world dominated by pharmacology. Other roles far removed from that of drug metabolism have been suggested.[4] Unless one takes a creationist or Lamarkian view, all mutations are Darwinian accidents, selected or not selected according to their benefit to the organism. What is initially an "accident" might over time become important, because it confers some advantage to the organism or because other critical processes may become adapted to, and dependent upon, it.

Goodman believes that little evolutionary "pressure" would have been brought to bear on the gas exchange of the otherwise fit adult. This is possibly correct, but our present level of health and longevity is evolutionarily recent; any advantage of coupling may be more apparent during early childhood development and in certain animals (perhaps those that hibernate). Coupling occurs in infancy as it does in adults; it is present in rats, guinea pigs and rabbits[5] and the work of Coleman suggests its presence in almost every mammalian species that he examined at London Zoo.[6] Although the lung structure did not evolve from that of gills, it is also interesting that Schoenlein in 1895 demonstrated the coupling of gill movements and heart beats in fish.[7] Plainly coupling is evolutionarily old and has persisted throughout the mammalia.

It is natural for us to attempt to ascertain the importance of coupling in the dynamics of human cardioventilatory control and to examine whether the process is of physiological benefit. By defining physiological advantage we move from basic science in the direction of clinical relevance. Correct or otherwise, it is surely desirable for a scientist to conjecture as to the meaning of an observation. Rather than "Beware of ascribing meaning to observation", we would prefer to read "We have tested Galletly and Larsen's hypothesis and found...".

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British Journal of Anaesthesia 1998; **81**: 109–110

BOOK REVIEWS

International Practice of Anaesthesia. C. PRYS-ROBERTS, B. R. BROWN JR (editors), J. F. MANN (consulting editor). Published by Butterworth-Heinemann, Oxford. Pp. 2337 (in two volumes); indexed. Price £195.00.

International Practice of Anaesthesia is heir to the highly successful *General Anaesthesia*, which was published in five editions between 1959 and 1989. It is likely to continue the success of its predecessor, as it combines the best qualities of *General Anaesthesia* with a considerable increase in size and the breadth of topics covered. The multinational authorship brings to the book a diversity of opinion and style which, in my opinion, puts its content well ahead of that of its major American rival. The preface by John Nunn includes, appropriately, a brief but moving tribute to the late Burnell Brown.

The book is divided into six sections: 'Basic Principles'; 'Systems of the Body', extensive reviews of the physiology, pharmacology, medicine, pathology and anaesthetic considerations relating to each major system; 'Obstetrics and Paediatrics'; 'Practical Anaesthesia', covering subjects not dealt with in Section 2; 'Acute Pain Relief'; and 'Monitoring and Anaesthetic Equipment', including statistics and computing. Division of each section into subsections makes it easy for the reader to locate chapters on subjects of interest from the list of contents; this is fortunate, because of the deficiencies of the index.

A major attraction of the book is the division of each subject into manageable quanta. The text is, for the most part, discursive and detailed, but because the authors were given tightly defined subjects, most of the chapters are relatively brief. This allows the reader to study a single topic in depth without 'information overload' or the need to read large amounts of irrelevant material. Many authors have written on subjects that closely match their expertise, and so can justify their comments and opinions with obvious ease. The quality of contributions varies but the general standard is excellent, and there is remarkably little overlap. Most chapters are liberally illustrated with tables and figures, and comprehensively referenced (range 4–282 references). The layout is clear.

The book is, in most respects, suited to the reader who seeks a detailed review of a specific subject, rather than a practical guide to clinical anaesthesia. This is not a criticism, as it was clearly the aim of the editors, and there are some excellent clinically directed contributions; the chapter on general management of the traumatized patient, for example, deals superbly with clinical management from the emergency room to the recovery area.

There are some surprising omissions. For example, although a chapter is devoted to total intravenous anaesthesia, I could find no mention of the concept of target-controlled infusion, and awareness during anaesthesia is considered only in relation to obstetric practice, although the incidence of awareness is higher in non-obstetric anaesthesia and the causes are usually different.

Now, some statistics: there are 234 contributors to the 167 chapters, which occupy 2337 pages in two volumes. The mean chapter length is 14 pages (standard deviation 5.1, median 13, range 5–41, mode 10). These values are rarely presented in book reviews. However, this book is different. Book reviewers are required to quote the total number of pages, and the pages of this book are numbered in an unusual style: volume/chapter/chapter page. To calculate the total number of pages, the reviewer must resort to a pocket calculator or computer spreadsheet, from which, of course, other statistical information can be derived with ease.

If the numbering system was devised to facilitate indexing, there are instances where it has backfired; for example, several references in the index to text in chapter 120 (volume 2; correct reference 2/120) have been indexed to volume 1, chapter 19 (1/19) (a double error; presumably chapter 120 was chapter 119 at some stage of production of the book). Indeed, the index is by far the most unsatisfactory feature of this book, and an example will illustrate the main problem. Look up 'Pulmonary gas exchange' and you will find that the subject is dealt with in volume 1, chapter 60, pages 1–13 (entitled, unsurprisingly, 'Pulmonary gas exchange'). Each of the 21 subdivisions under the heading of 'Pulmonary gas exchange', refers to one or more of the 11 pages that comprise the text of Chapter 60 (pages 12 and 13 contain the list of 105 references). There is no indication in the index that the term 'pulmonary gas exchange', or any of the key words in its subdivisions, occur in any other part of the book, although these subjects are dealt with extensively in other chapters. Listed under 'Postanaesthetic recovery', a topic discussed extensively in several chapters, are 27 references to the chapter of that name but none to any other part of the book; searching under 'Diagnostic procedures' yields a similar result. Search under 'Shunt' and you will find only references to 'Shunts' (as in congenital heart disease). Search under 'Ventilation–perfusion' and you will find nothing.

Such a poor index is all the more unfortunate in a book that will be used primarily as a reference text, and is competing with a rival available on CD-ROM, currently the ultimate book search tool. This deficiency does not detract from the quality of the text, and there is no doubt that this book deserves a place in every departmental library. The editors of *International Practice of Anaesthesia* have produced a worthy heir to its predecessor, but the publishers should have done better.

A. R. Aitkenhead

Brain Edema X (Acta Neurochirugica Supplement 70) (Proceedings of the 10th International Symposium on Brain Edema, October 20–23, 1996, San Diego, California, USA). H. E. JAMES ET AL. (editors). Published by Springer, NewYork. Pp. 302; indexed; illustrated.

This book is a compilation of papers presented at the 10th International Symposium on Brain Edema held on October 20–23, 1996 in San Diego, California. Although papers were subject to peer review the rejection rate was low, and more than 90 of the 100 papers submitted were accepted for presentation and publication. The compilation provides a comprehensive and up-to-date reference on the disease processes associated with brain oedema. Each of the nine sections deals with a particular aspect of brain oedema, from ischaemia to changes in the blood–brain barrier. Although most of the work presented is experimental, with papers more like extended abstracts than true, "full-length" manuscripts, some of the papers published deal with therapies that have, or soon will have, clinical implications. For example, Hartl and colleagues (pp. 40–42) illustrate how the administration of mannitol to head-injured patients with intracranial hypertension improves cerebral perfusion pressure but fails to increase cerebral tissue oxygen. This raises questions about targeted cerebral perfusion pressure therapy as a sole goal of treatment in the head-injured patient. However, as the book is a comprehensive guide to research in progress on topics related to brain oedema, it will undoubtedly be found in the libraries of departments with a heavy commitment to basic science research related to brain dysfunction.

B. Matta

Baillière's Clinical Anaesthesiology (Vol. 10, No. 4). Paediatric Anaesthesia. S.G.E. LINDAHL (editor). Published by Baillière Tindall, London. Pp. 776; indexed; illustrated. Price £30.00.

This edition of Baillière's regular collection of reviews is on paediatric anaesthesia. As usual, the contributions are truly international, but with a bias towards Europe. The result is a collection of chapters, each of which can be read separately, touching on disparate areas. There are sections on perioperative medicine and operative medicine, and a single chapter on intensive care. The chapters on working with parents and PONV are a little short and therefore incomplete, but the update on regional anaesthesia is very readable, with a comprehensive review of the literature on extradural opioid use. The final chapter, on severe trauma, is not sufficiently comprehensive to be of use to examination candidates or those involved regularly in this area.

As a whole, the text is rather dry, with a paucity of illustrations. Individuals may not want to buy this book as many libraries keep the series, although there is much of interest for specialist anaesthetists. However, I believe many clinicians will not find that this volume fills the gap between textbook and journal.

I. Wilson

Key Topics in Chronic Pain. K. M. Grady and A. M. Severn. Published by: BIOS Scientific Publishers, Oxford. Pp. 193; indexed. Price £17.95.

This book is the latest in the Key Topics series, the format of which is short synopses arranged in alphabetical order. Forty-five topics are covered, with one to four pages devoted to each, and the book is written by two consultant anaesthetists responsible for running pain clinics, with contributions from a neurosurgical colleague. The authors state that it is a working manual, designed for specialist registrars, general practitioners, psychologists, nurses and physiotherapists.

Despite the advances in our understanding of pain physiology, there are few controlled trials to govern the management of clinical problems in this challenging group of patients. The authors acknowledge this, and have devised a system whereby the extent to which a statement is based on scientific evidence is readily communicated to the reader. Statements are classified as being derived from one of three main sources: 1) systematic reviews of randomized controlled trials; 2) randomized trials alone; or 3) uncontrolled trials or case histories.

The chapters are generally of a consistently high standard. Several of them cover pain neurophysiology, and useful references to basic sciences throughout the book provide a useful backdrop. The chapter given over to examination and elicitation of nerve-root signs is concise, comprehensive and commendable for its simplicity. The chapters that detail the principles of regional blockade, both somatic and autonomic, commonly used in this specialty are a useful overview, but insufficiently detailed to constitute a manual for anyone undertaking such procedures. The four chapters given over to pain associated with malignancy, where different considerations prevail, reflect the contribution that a specialist in the management of chronic pain can make to palliative care

Throughout the book there is a strong emphasis on the psychosocial, behavioural and emotional approach to the patient afflicted with chronic pain. Two chapters address these issues, one discussing the assessment of these factors in the pain clinic and the other describing the principles of pain management. The weakest sections of the book are those dealing with the pharmacological aspects of chronic pain management. The description of the analgesic ladder is somewhat lame, and there is an imbalance in the space and consideration given to particular agents — for instance, there are two lines on the role of tramadol in the pain clinic, but an entire chapter on ketamine. It seems that the authors' enthusiasm for certain drugs has obscured the reality of established practice.

Chronic pain as a specialty lends itself less easily than the subjects of other volumes in the Key Topics series to alphabetical arrangement, and some of the information comes across in a rather disjointed manner. For example, the chapter headed 'The sympathetic nervous system and pain' includes a description of the pharmacological agents often used in this area but makes no reference to the interventionist therapeutic measures available; these appear under 'Nerve blocks — autonomic'. In this respect some of the headings are rather contrived. Nevertheless, there are many topics such as complex regional pain syndromes, neuromata and post-incisional pain, post-amputation pain, post-herpetic neuralgia and trigeminal neuralgia that easily fit this structure and all are well written. It is surprising that the authors could find no place for coccydynia, a relatively common pain problem that would have neatly fitted this format. The chapter concerning spinal cord and brain stimulation is outstanding.

For all our criticisms, this book is a thoroughly enjoyable read. It is engaging, informative and forms a solid foundation for the taking up of more detailed texts We thoroughly recommend it for trainee anaesthetists preparing for the final FRCA — it will more than satisfy your requirements. In addition, for those considering a career in chronic pain, this is an excellent opener.

L. S. Gaspar
A. A. Leach

Alternate-site Anaesthesia (Clinical Practice Outside the Operating Room). G. B. Russell (editor). Published by Butterworth-Heinemann, Newton, MA, USA. Pp. 482; indexed; illustrated.

As its title suggests, this book is dedicated to anaesthesia in locations other than the operating theatre. It is laid out in 24 well referenced chapters, with plenty of illustrations and tables breaking up the text and making the book easy to read. The book opens with a general discussion about the various environments encountered, the indications to use them, and the necessary equipment and anaesthetic techniques. The importance of equipping alternative sites to the standard of, and in the same way as, the operating theatre is pointed out. Also discussed are concerns about working in isolation without skilled assistance, which highlight the need for anaesthetists to participate in the planning of such facilities. The book then principally looks at anaesthesia in the X-ray department, providing a good review of each type of imaging technique and the problems posed for the anaesthetist. It considers the provision of anaesthesia within intensive care, radiotherapy and psychiatric units, in cardiac catheterization laboratories and emergency rooms, and in the outpatient clinic. The final chapters deal with military anaesthesia and teleanaesthesia. The latter paints an interesting picture for the future of remotely controlled anaesthesia, using computer technology to communicate with distant anaesthetic technicians and machines.

Chapters 3–12 are radiologically based, with radiological and anaesthetic considerations split into separate chapters for CT, MRI and interventional vascular, non-vascular and neuroradiological procedures. The inevitable problem with these chapters is repetition of the basic principles, which are, in general, better covered in the radiology chapters than in the anaesthetic ones. The physics for MRI is perhaps a little intense, but does explain very well why there are specific problems. Unfortunately, the accompanying anaesthetic chapter is a little disappointing, and left me wondering if the author had ever given an anaesthetic in the MRI environment.

Chapters 10 and 11 on interventional neuroradiology stand out as excellent reviews of this rapidly developing area of minimally invasive treatment for neurovascular problems. I recommend them to anyone interested in these techniques. Other chapters of note are 13, a clear review of anaesthesia for ECT, and 15, a concise look at the role of the anaesthetist in the emergency room. The contribution on interventional radiological vascular techniques is interesting, although the emphasis on percutaneous portocaval shunting is perhaps excessive, considering the omission of such major endovascular techniques as thoracic aneurysm stenting, which have a potentially wider application and very interesting anaesthetic techniques. The remaining chapters provide a comprehensive overview of their topics, giving a good starting point for reference.

As this is an American text (beware spellings, and drug names) it is aimed at anaesthesiologists for whom, unlike their counterparts in the United Kingdom, anaesthetic work outside the operating room is a relatively new development. However, it provides a relevant and up-to-date review of most of the areas and-procedures requiring anaesthetic cover outside the operating theatre. I recommend the book as a useful reference text for a departmental library or interested individual.

I. E. Tweedie

British Journal of Anaesthesia 1998; **81**: 111

ERRATA

*Myocardial ischaemia after coronary artery bypass grafting: early vs late extubation (BJA; **80**: 20–25)*

An author's error occurred in last sentence of the first paragraph of the section entitled Patients and Methods – peroperative management. The sentence should read:

"At the end of surgery, Group E patients were given neostigmine 0.03 mg kg^{-1} and glycopyrrolate 0.006 mg kg^{-1} to reverse neuromuscular blockade."

*Leucocyte distribution during sevoflurane anaesthesia (BJA; **80**: 502–503)*

An editorial error occurred in the Methods and Results section of this paper (2nd column, 3rd paragraph, 1st sentence). The sentence should read:

"Mean age of the study population was 31.8 (range 20–55) yr."

We would like to apologise for this error.

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

"Old ideas, new applications"

Fashions come and go within anaesthesia, sometimes subsequent to the introduction of new drugs or techniques, and sometimes because of the changing demands of surgery. As anaesthetists have always required apparatus to practise their art, the progress of anaesthesia has closely followed technological advances. An active History of Anaesthesia Society and numerous collections of outdated apparatus indicate that historical interest in the activities of previous colleagues has always been strong. Many "new" developments are little more than a revisitation of a technique which has been popular in the past and has been exhumed by a group of enthusiastic individuals.

The birth of regional anaesthesia came in the 1880s when the German ophthalmologist Carl Koller, dissatisfied with the operating conditions provided by general inhalational anaesthesia, discovered that, by dripping a solution of cocaine into the conjunctival sac, painless surgery could be carried out on the eye. This concept was developed by William Halsted, a dynamic American surgeon who, with his colleague R S Hall, performed the world's first documented nerve block on his own mandibular nerve.[1] His enthusiasm for self-experimentation established the principle that many nerves were accessible to local anaesthetic block, but his subsequent cocaine addiction graphically illustrated the dangers of this particular drug. When Ernest Fourneau manufactured stovaine (*fourneau* is French for stove!) and Alfred Einhorn developed procaine (novocaine), both of which were considerably less toxic than their predecessor, enthusiasm for what was then known as "conduction anaesthesia" blossomed, and with Heinrich Braun's publication of the classic text *Local Anaesthesia* in 1905, it entered mainstream practice.

At this stage, regional anaesthesia was generally used as an alternative to general anaesthesia, often to allow surgery on patients considered too frail for the rigours of ether inhalation.

Elsewhere in this issue, Richardson and Lonnqvist review the applications and techniques of paravertebral block.[2] It appears that an early use of this block was to permit the operation of thoracoplasty, carried out in an attempt to halt the progression of pulmonary tuberculosis.[3] The benefits of avoiding deep ether anaesthesia or the possibility of cardiovascular collapse with spinal anaesthesia in this group of patients are obvious, although undergoing major thoracic surgery with a one-sided paravertebral block cannot have been an enticing prospect for the patients themselves. Sherwood-Dunn wrote in 1920: "The patient may ... complain if he hears the section of the ribs; it is therefore well to cut the ribs gently and to stop the patient's ears. A little girl 11 years of age ... upon whom we did a resection of 3 ribs for interlobar empyema, cried every time she heard the cutting of a rib, though she had not complained once during the remainder of the operation...".[4]

Paravertebral blocks interrupt both the somatic and visceral components of the nervous system, and it was soon realised that this technique could be used for pain relief as well as providing anaesthesia for surgery. In the 1920s paravertebral block became a popular treatment for intractable angina pectoris.[5] In 1933, J. G. P. Cleland described T.11 and T.12 paravertebral nerve blocks for the relief of labour pain.[6]

With the introduction of novel anaesthetic agents such as the neuromuscular blocking drug, curare, and later halothane, different approaches to the management of at-risk patients superceded the old methods. The changing pattern of disease also played its part in altering the demands placed on anaesthetists by their surgical colleagues. A further blow to the enthusiasts of regional anaesthesia was delivered by the tragic cases of Woolley and Roe in October 1947. Permanent nerve damage followed the spinal injection of cinchocaine which had been contaminated by the phenol used to sterilise the outside of the glass ampoules in which it was contained.[7]

However, the emergence of pain relief as a sub-specialty of anaesthesia in the 1960s has resulted in the "rediscovery" of many of the regional techniques which were popular decades earlier. With advances in understanding of the pathophysiology of chronic pain, the links between anatomical appreciation, clinical medicine and basic science are provided by our observations of what happens in humans when a particular part is temporarily denervated. This has both diagnostic and therapeutic value.

Paravertebral blocks are simple, quick and safe to perform. The nerves that pass through the paravertebral space encompass the thorax and abdomen in the thoracic region, and the lower limbs in the lumbar region. In the thorax, the sympathetic chain lies anterior to the articulations of the ribs with the transverse processes.[8] In the lumbar region, it is even more anterior.[9] In both areas, the white and grey rami communicantes traverse the paravertebral space.[10] Thus, when local anaesthetic is injected into the paravertebral space, both somatic and visceral afferent and efferent activity is interrupted. That there is a neural link between soma and viscera is incontrovertible. The nature of that link is the subject of much theorizing, debate and dispute. There are many documented accounts of visceral pathology producing somatic pain and, in the longer term, measurable somatic pathology. There are reports of the quaintly named shoulder-hand syndrome (complex regional pain syndrome type I) developing after myocardial infarction,[11] and the phenomenon of fibromyalgic bands developing in periscapular musculature in sufferers of angina pectoris.[12]

Every chronic pain clinic in the United Kingdom surely has a retinue of patients with unexplained abdominal pain who have undergone extensive investigation which has failed to demonstrate any gross visceral pathology. Their accounts of the pain clearly place their symptoms into the category of those with a visceral origin. As a diagnostic tool, if nothing else, the capacity to temporarily denervate the suspected organs necessarily forms part of the assessment of the complainant's symptoms. Indeed, in some situations, a visceral block may result in long-term symptom relief. In one recent series, a substantial proportion of intractable angina sufferers achieved complete pain relief for at least one month after temporary cardiac denervation via either stellate ganglion block or thoracic paravertebral block with a single injection of local anaesthetic (M Chester: personal communication). These techniques provide the chronic pain clinician with a link between science and clinical practice.

With our current understanding of pain processing, both peripherally and centrally, these observations can be baffling. Most pain research has centred on the perception of somatic pain which, in physiological terms, is a more easily comprehensible phenomenon. If a body part is placed into a situation which compromizes the well-being of its tissues, an unpleasant sensory and emotional response to the threat of tissue damage can only be of benefit. The severity of discomfort perceived in response to an unpleasant stimulus is reproducible. This has been established by painstaking study of the most accessible part of the pain perceiving apparatus, the cutaneous polymodal nociceptor, first postulated by Sherrington in 1906.[13] But it is a failing of pain research that the assumption has often been made of the universal nature of this receptor. It is clear that neither the functions nor adequate stimuli are known for the majority of visceral afferent fibres.[14] There is a lack of hard data to support the hypothesis that visceral pain processing is the same as somatic perception; indeed, it would seem that visceral pain mechanisms are radically different to those at the periphery, with "intensity-encoding" populations of neurones rather than specific pain receptors.[15] Of what biological or evolutionary value is the perception of visceral pain? The severity of visceral pain, as previously mentioned, often bears no relation to the extent of disease. Animal studies of visceral pain have centred on the gastrointestinal and genitourinary tracts, and are limited to neurophysiological recordings of activity after pathological distension or chemical irritation of hollow viscera.[16] Human studies are obviously restricted by lack of access to visceral nerves, and depend on a reported change of symptom severity, a necessarily subjective end-point. Because of the difficulty in defining suitable control groups, and ethical difficulties in assigning placebo treatments to pain sufferers, there is a lack of properly constructed controlled trials among chronic pain patients.[17] Clearly, many of the documented observations can only be incompletely understood with our current knowledge, and much work remains to be done.

The combination of somatic and autonomic nerve block achieved by paravertebral injection of local anaesthetic is patently of benefit when treating postoperative pain after unilateral abdominal or thoracic surgery. Techniques are described of infusion analgesia with a catheter placed in the paravertebral space.[18] Indeed, bilateral catheters may be sited for pain-relief after major abdominal surgery.[19] This may be a preferable alternative to extradural infusion analgesia, with its well-documented drawbacks of postural hypotension and urinary retention.[20]

The most recent anaesthetic drug releases from the pharmaceutical companies suggest that there is a desire for agents of considerable but predictable potency whose effects appear rapidly and whose elimination from the body is also rapid. Drugs such as propofol, alfentanil and atracurium started the trend, and the recent introductions of sevoflurane, desflurane and remifentanil support the conjecture that rapid recovery from general anaesthesia is something the practising anaesthetist desires. There is certainly something awe inspiring and magical in the properties of these latest offerings that allows us to converse with the patient a short while after their operation. However, if a patient who has recently undergone surgery is to awaken clear-headed and oriented minutes after the cessation of surgery, the anaesthetist has a responsibility to ensure that the rapid return of consciousness is accompanied by a freedom from pain. There seems little logic in using a drug such as remifentanil intraoperatively to suppress the surgical response to painful stimulus, only to allow the patient to regain his senses, acknowledge that pain is severe and then obtund consciousness once more with large doses of a long-acting opioid.

This, surely, suggests a new role for such procedures as paravertebral blocks. As a "one-off" injection it can be carried out at the end of minor or intermediate surgery to ensure maximum duration of effect. If a catheter technique is to be used, this may be sited before surgery, either before or after induction of anaesthesia, according to the wishes of the patient or anaesthetist, and used as the sole analgesic, peroperatively and postoperatively, avoiding the use of opioid drugs altogether if this is considered desirable.

With the evolution and advancement of anaesthesia, there is much to be learned from the pioneers and experimenters who preceded us. Their skills and observational abilities should not be belittled merely because their methods were sometimes flawed and their equipment more primitive than that of today. It is important that we preserve their knowledge and use it wisely, not only for the benefit of our patients, but also for those students, doctors and scientists who will follow in our footsteps. The retention of regional anaesthetic skills such as paravertebral block is an essential part of that preservation.

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EDITORIAL II

Dynamic hyperinflation—the anaesthetist applying a tourniquet to the right heart

> *"The leperous distilment; whose effect holds such an enmity with blood of man that, swift as quicksilver, it courses through the natural gates and alleys of the body,...."*
>
> *Hamlet*, Act 1 Scene 5

Even though the play antedates the publication of *De Motu Cordis* by nearly 30 years, the quotation was used as evidence that Shakespeare was familiar with William Harvey's concept of circulation of blood.[1] There has been a tendency for clinicians to underrate the importance of the right heart[2] to flow "*through the natural gates and alleys*". Transoesophageal echocardiography is opening a window under operative conditions and through it can be seen, in a way previously not possible, the changes of preload and afterload on atrial, ventricular, tricuspid valve and outflow tract function.[2] Functionally, lying in a Russian doll's nest of anatomic and pressure layers, the right heart is weakened by being juxtaposed between the muscle- bound left ventricle and the lungs, and is sensitive and vulnerable to disease of both these organs and the pericardium. Anaesthetic insults primarily act on the myocardium and pulmonary vasculature but, by taking control of the airway with a tracheal tube, an anaesthetist breaches the integrity of, and imposes forces, that markedly influence the climate of the intrapleural layer. Additional, supranormal pressures of positive pressure ventilation (IPPV) may be enough to override the protective cushioning of the pericardium so that the right heart is compromised; sometimes, particularly in those with a predisposing pathophysiology, this effect is critical.

Ultimately, it is intra-alveolar pressure within the intrapleural layer that dictates forward flow of blood through the lungs. It is pathologically raised in several well known states encountered by anaesthetists. If expiratory airflow obstruction occurs then intra-alveolar pressure may remain positive throughout much of the respiration cycle. This *auto* or intrinsic PEEP (PEEPi) effect,[3] is typically part of acute and chronic obstructive airways disease, notably asthma and emphysema, and of adult respiratory distress syndrome.[4] Recently introduced treatment options for respiratory failure like lung transplantation,[5] minimal access thoracic surgery[6] and lung volume reduction[7] have swelled the ranks of the predisposed and susceptible. Large airways, too, can be dysfunctional such that PEEPi is generated: classically, for example, in the presence of inhaled foreign bodies, and central airways compression.[8]

To the list of primed can be added diverse causes of accidental expiratory retardation engendered by the processes of anaesthesia, such as obstructed ventilator tubing; faulty anaesthetic circuits; wet humidifying filters[9]; narrow tracheal tubes, notably double lumen tubes[10]; and inappropriate ventilation techniques.[11, 12] The latter can lead to barotrauma and the peculiar manifestation of pulmonary hypercompliance in a relatively non-compliant chest cavity, known as dynamic hyperinflation (DHI).

The imposition of IPPV may produce the increased pressure dynamic that results in a tamponading constrictive force being applied to the right heart; a "tourniquet effect" as gas is trapped by increments and successive breaths become, what is appropriately described as "stacked" with a net positive balance of gas. Cardiac sensitivity to the additive pressure effects of IPPV may result from the fluid dynamic changes of hypovolaemia, vasodilatation, superior vena cava obstruction and pleural or pericardial effusions.

Of the three current defined variants of PEEPi [13]—dynamic, occlusion and static—the latter are measurable easily in mechanically ventilated patients in intensive care units.[14–16] But from the operating table-side, the anaesthetist is most likely to be forewarned of the development of a compromising level by having a high index of suspicion and using right heart signs as surrogate barometry.[2, 17] A raised external jugular venous pressure and a fall in systolic arterial pressure are a common experience for most anaesthetists when anaesthesia is induced in chronic bronchitic patients and, though these usually resolve, such signs alert us to the risk of compounding PEEPi with deliberate or accidental PEEP. Arterial wave forms in the invasively monitored patient,[18] by reflecting *pulsus paradoxus*, can also be a warning sign, as is a combination of oxygen desaturation and a fall in arterial pressure, as sensed by some forms of pulse oximeter.[19] A deliberate manoeuvre of disconnecting the ventilator may be the ultimate test. A commensurate improvement in oxygen saturation and arterial pressure is virtually diagnostic of DHI being part of the pathophysiology; it should signal the use of a suitable ventilatory pattern.[17]

The best ways of reducing the constricting effects of DHI are by treating the various components logically. In so doing, the development of DHI should be pre-empted in some of the recognizably predisposed. Induction of anaesthesia with agents with venous constrictive activity, such as etomidate or ketamine (Feneck, personal communication), may be rational. Right heart support has received little coverage but the judicious use of colloid volume to optimize venous return, the use of inotropes to adjust venous tone and myocardial contractility, and agents that influence the pulmonary circulation all have a place theoretically.[20] Influencing the airways should be considered in some cases. If there is evidence of reversibility or reactivity, small airways dysfunction may respond to bronchodilators or corticosteroids. In cases with central airways obstruction, which cannot physically be removed, consideration may need to be given to the use of tracheal or bronchial stents. The insertion of drainage systems will help in the event of emphysematous bullae expanding[17] or the cases in which pleural or pericardial effusions are present.

But it is ventilation stratagems that are the mechanisms by which anaesthetists can counter PEEPi.

These should hinge on low-peak inflation pressures, prolonged expiratory intervals,[6] and minimizing mean intrathoracic pressure.[17] The deliberate addition of PEEP is a vexed question. As a general rule, PEEP is counter-productive, but in patients with collapsing small airways the internal splinting effect to maintain patency throughout the respiratory cycle may allow a reduction in the volume of trapped air.[21] This process, part of optimization of PEEP, is usually not an option in the acute situation and more applicable to longer term management of acute lung injury in intensive care units. But optimal PEEP may counter some of the effects of the use of double lumen tubes in which a small unilateral lumen may contribute to the development of air trapping[10] in patients undergoing surgery for respiratory failure.

Is DHI a problem that should concern anaesthetists working outside environments commonly dealing with the predisposed? There are scattered reports of unexpected cardiac arrests and fatalities in the literature.[22–24] The common theme of suddenness and the suspected presence of conditions associated with a increased PEEPi are strong evidence that DHI is part of the story, and that it is a phenomenon that should be more widely recognized by both those administering anaesthetics and those involved in resuscitation.[23] Standard guidelines for resuscitation recommend manoeuvres that would be counter-productive in the event of gas trapping that is sufficient to impede right heart function.[23]

Some personal knowledge of two unexpected deaths, in which embolic phenomena were suspected as causative because right heart dysfunction was an agonal event, but in which the working diagnoses could not be substantiated with angiography or at postmortem examination, would fit a hypothesis that DHI is the guise of a "*leperous distilment*" that can kill without leaving a pathological imprint. More chronic forms of air trapping lead to changes that are detectable histologically,[25] but the cessation of ventilation as the preterminal event in an acute situation would allow lung deflation so that the crucial *prima facie* evidence, that of hyperinflation, would disappear. In the absence of any other explanation, it is appropriate to advise that if DHI is at all possible, then the disconnecting of the ventilator or stopping ventilation, albeit at an apparently critical moment during such a highly charged scenario as a cardiac arrest, may be life-saving. Such a manoeuvre would facilitate venous return and improve cardiac output.[26] As an *aide mémoire*, adjust the old adage of presumed oesophageal intubation ("if in doubt, take it out") to "if in doubt, let it (*the trapped gas*) out"; or, alternatively, "save a life, allow to expire!"

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EDITORIAL III

Mathematical coupling in medical research: lessons from studies of oxygen kinetics

It is common practice in medical research to investigate the relation between two physiological variables by obtaining pairs of measurements over a range of values and then plotting one variable against the other. The nature of the relation may be examined using a technique such as regression analysis, and the strength of the relation assessed by calculating the correlation coefficient. It is often assumed that when a correlation is found between the variables they are physiologically related in some way. In some situations this may not be correct.

Two variables, each of which is dependent on a third variable which may not be known, can correlate even if not causally linked. For example, unrelated variables that both change with time will correlate. Another cause of spurious correlation is illustrated in figure 1. A random number table was used to generate 50 pairs of numbers, $x_{(n)}$ and $y_{(n)}$, between 1 and 10. When these numbers are plotted against one another a random scatter of points is produced and, as expected, the correlation coefficient is 0 (fig. 1A). If the same pairs of numbers are used to calculate a third variable $x.y_{(n)}$, the product of each data pair, $x_{(n)}$ re-plotted against $x.y_{(n)}$ is no longer random. Instead, there is a linear relation with a correlation coefficient of 0.7 and a slope that is statistically different from 0 (fig. 1B). This surprising result occurs because the values of $x_{(n)}$ are present in both variables ($x_{(n)}$ and $x \times y_{(n)}$), which are then linked mathematically. A similar result occurs when variables are derived by addition, subtraction, or division. This is *mathematical coupling*.

There are many situations in medical research, and in the clinical management of patients, when physiological variables that are difficult to determine directly are calculated from other more easily measured variables. The formulas required are derived from basic physiological principles. Examples in anaesthesia include the deadspace ratio derived from arterial and mixed expired carbon dioxide partial pressures using the Bohr equation, and systemic vascular resistance derived from cardiac output and mean arterial pressure. If the relation is investigated between a derived variable and another variable that is either a component of the derived variable or shares a component with it, the relation may be affected by mathematical coupling. As a result, part or all of the relation may be spurious. Mathematical coupling can occur if paired values for physiological deadspace ratio and arterial carbon dioxide tension, or cardiac output and systemic vascular resistance, are plotted. The confounding effects of mathematical coupling were first pointed out by Archie in 1980[1] but despite his description, this phenomenon has continued to confuse medical research and is often unrecognized or poorly understood.

A fundamental difference between pairs of random numbers and pairs of physiological data is that the latter may be truly physiologically linked. For example, if paired measurements of cardiac output and arteriovenous oxygen content difference are plotted against one another, a negative correlation might be expected because, under conditions of constant oxygen consumption, increased oxygen delivery to tissues results in decreased oxygen extraction. The product of cardiac output and oxygen difference can be used to calculate oxygen consumption using the Fick principle. In many studies, the relation between oxygen delivery and oxygen consumption has been examined using this method, particularly in the critically ill. Mathematical coupling affects this relation because the cardiac output and arterial oxygen content are used in the calculation of both variables. In many studies in critically ill patients, correlation between oxygen delivery and consumption was thought to indicate an oxygen supply dependency. In these studies it was not clear to what extent this finding was an artefact attributable to mathematical coupling, and this is a subject of considerable controversy. Several recent studies have shown how mathematical coupling operates in oxygen kinetics.[2 3] A consideration of these, and other relevant work, allow the formulation of guidelines that are applicable to situations in clinical practice or in medical research in which mathematical coupling may occur.

Mathematical coupling is most likely to bias the true relation between two variables which share components if the relation is distorted by non-physiological factors, and then plotted values behave increasingly like the randomly distributed numbers of figure 1. Several mechanisms cause this tendency to randomness in physiological studies. First, if the accuracy of measurement is low, random errors increase the spread of the data, and if the variables have common components they will share the measurement errors associated with those components. Second, if several data from many individuals are combined, the true physiological relation present in an individual patient may be obscured. In either situation, mathematical coupling may cause an artificial correlation. These two processes will be considered in more detail.

Any physiological measurement is subject to measurement error. When the relation between two variables is plotted, large measurement errors increase the scatter of the data making them more random. When these variables have shared components, mathematical coupling of the random errors in both variables can produce a correlation obscuring or changing the true physiological relation. This is most likely when a physiological variable is derived from a number of separate measurements, which makes it almost inevitable that its accuracy is low. For example, arteriovenous oxygen difference is calculated from measurements of haemoglobin concentration, oxygen saturation and oxygen tension in both arterial and mixed venous blood. The errors in these measurements may propagate to make the accuracy of

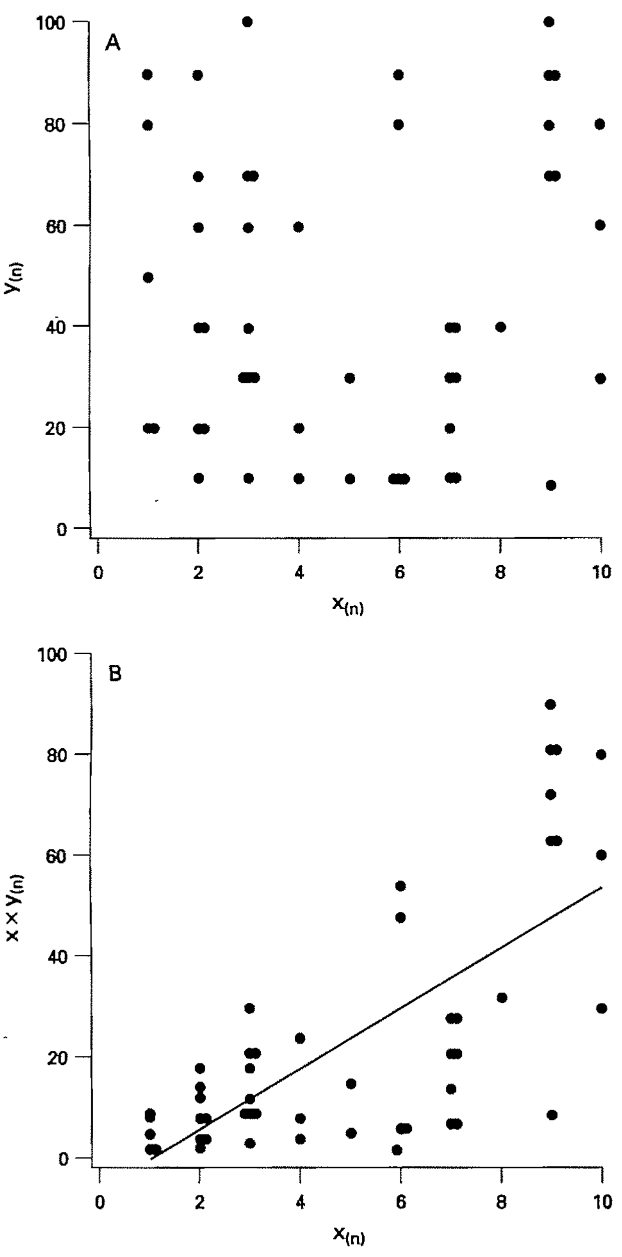

Figure 1 (A) Plot of 50 pairs of random numbers, $x_{(n)}$ and $y_{(n)}$, between 1 and 10. (B) Using the same random number data pairs, a third variable $x.y_{(n)}$, the product of $x_{(n)}$ and $y_{(n)}$, is positively correlated with $x_{(n)}$ when re-plotted. This occurs because of mathematical coupling.

the final oxygen difference calculation low.[4] In medical studies, we often look at changes in variables in response to a treatment. The relevance of a change in a variable cannot be assessed if the accuracy of measurements is not known or is not reported, because the change could simply represent random variation. When used appropriately, statistical methods allow for the randomness in a measurement resulting from differences between individuals, or from random errors in the actual measurements. However, even appropriately used statistical tests cannot detect or compensate for the spurious relation produced by mathematical coupling of shared errors. For example, if a study design unintentionally favours one direction (positive or negative) of error, the chance of a spurious correlation is very high. This might occur if the coupled variable is manipulated in a study until a particular positive change is observed (for example, if cardiac output is manipulated during an oxygen kinetic study). If the positive end-point means that more positive than negative errors are included in the analysis, these errors apply to both variables under investigation. This can result in a positive relation caused entirely by mathematical coupling. In this situation, a correctly applied correlation test or regression analysis supports the relation, but the relation is an artefact.

The influence of measurement errors on a relation is reduced by increasing the number of points plotted. A common problem in studies liable to bias by mathematical coupling is that there are too few data pairs over too narrow a range of values. This was frequently so in early studies of the oxygen supply-demand relation in critically ill patients: in many studies there were only two data pairs, one before and another after an intervention that itself induced only small alterations in oxygen delivery. Bias caused by mathematical coupling is reduced by studying large changes in the variables of interest and plotting a wide range of values. Stratton and colleagues proposed a statistical method to correct for the effect of mathematical coupling error, which relied on estimating the accuracy of measurements of shared components, and the reliability of any changes observed in them.[5]

Pooling data from different subjects increases the chance of a spurious correlation when there are shared variables.[6] This is particularly likely if data from many patients are combined and then analysed, instead of examining each patient individually, or using a single summary statistic from each patient. Pooled data are more widely scattered than points plotted from a single subject because of interindividual physiological differences. As the scatter widens, it behaves more like the data in figure 1 and has a greater tendency to bias by mathematical coupling. The importance of this source of error in oxygen kinetic studies was shown by Phang and coworkers, who found that there was no relation between oxygen delivery and consumption in most individual patients, but when data from all patients were pooled there was a positive correlation between the variables.[3]

In the critical care literature, there is no doubt that mathematical coupling has confused the interpretation of oxygen kinetic studies in which the Fick method was used to calculate oxygen consumption. Recent studies in which analysis of respiratory gases was used to measure oxygen consumption directly, which avoids mathematical coupling altogether, have found little or no evidence of a dependent relation between oxygen delivery and consumption.[2,3,7,8] It is clear from these studies that when oxygen consumption is calculated by the Fick method, mathematical coupling causes a positive correlation between oxygen delivery and consumption that is either entirely artefactual, or much stronger than it really is.

The use of derived physiological variables in medical research and in clinical practice is widespread and sometimes unavoidable. Inevitably there are occasions when mathematical coupling will influence the relation between two variables. We suggest some guidelines drawn from oxygen kinetic studies which are applicable to other areas of medical research (table 1). A greater awareness and understanding of the pitfalls of studying the relation between variables with shared components should reduce the risk of

Table 1 Features of study design to reduce the likelihood of mathematical coupling error

(1) Avoid coupling of variables by using alternative methods of measurement whenever possible.
(2) If there are shared variables, predict the likely direction of bias resulting from coupling and make this clear when interpreting the results.
(3) Estimate and state the accuracy and repeatability of physiological measurements and calculated variables, under the conditions of the study. This will enable an estimation of reliability of any physiological changes. When the repeatability of measurements is low, interpret mathematically coupled data with caution.
(4) Collect as many pairs as possible over the widest possible range of values.
(5) Ensure study designs do not select for one direction (positive or negative) of measurement error.
(6) Avoid pooling data from many subjects; instead, describe relations in individual subjects or use a single summary statistic from each subject.
(7) Whenever possible, apply statistical methods that correct for the effects of mathematical coupling.

erroneous conclusions in future studies, and avoid repetition of the confusion and controversy that has dogged oxygen kinetics.

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CLINICAL INVESTIGATIONS

Thoracic and lumbar extradural structure examined by extraduroscope

T. IGARASHI, Y. HIRABAYASHI, R. SHIMIZU, K. SAITOH AND H. FUKUDA

Summary

We examined the extradural space using a flexible extraduroscope in 113 patients undergoing extradural anaesthesia. Patients were classified into two groups to receive either thoracic or lumbar extradural anaesthesia as needed for perioperative analgesia. The extraduroscopy showed that the thoracic extradural space becomes widely patent after injecting a given amount of air and that the amount of fatty and fibrous connective tissue is less in the thoracic extradural space compared with the lumbar extradural space. We suggest that differences between the structure of these two vertebral regions may affect the spread of local anaesthetics in the extradural space. (*Br. J. Anaesth.* 1998; **81**: 121–125)

Keywords: anaesthetic techniques, extradural; anatomy, extradural space; measurement techniques, extraduroscope

Many investigators have described differences in dose requirement of local anaesthetics depending on the site of injection for extradural anaesthesia.[1–4] Several authors have reported a reduction in thoracic dose requirement compared with lumbar extradural dose requirements.[5 6] However, the reasons for this reduction in thoracic dose requirement have not been thoroughly investigated. Several factors may contribute to the different dose requirements, including the size of the underlying nerve roots,[7 8] the thickness of their coverings[5] and the negative intrapleural pressures.[3] Differences in the anatomy of the extradural space associated with the vertebral regions may affect the spread of local anaesthetics. Some of these factors have been assessed by magnetic resonance imaging[9] or the direct measurement of extradural pressures.[10] As extraduroscopy can provide a clear view of the extradural space,[11–13] we used this technique to investigate the differences in the structure of different regions in the extradural space.

Patients and methods

This study was approved by our Local Ethics Committee and informed consent was obtained from all patients. We examined the extradural space with a flexible fibrescope in 115 patients undergoing extradural anaesthesia for a variety of surgical or therapeutic procedures including hysterectomy, oophorectomy, knee arthroscopy, total knee arthroplasty, total hip arthroplasty, transurethral resection of the prostate, transurethral resection of bladder tumours, thoracotomy and upper and lower abdominal surgery. Patients with a history of previous extradural anaesthesia, pregnancy, neurological disease, abnormalities of vertebral column or abdominal distension were excluded. Patients were classified into two groups according to the site of the extradural anaesthesia as needed for perioperative analgesia: the thoracic group (n=63) and the lumbar group (n=52). The extradural anaesthesia was carried out between the Th7 and Th10 in the thoracic group and L2–L3 interspace in the lumbar group.

Each patient was premedicated with hydroxyzine 25 to 50 mg and atropine 0.25 to 0.5 mg. The patient was placed in the right lateral decubitus position on a horizontal operating table. A 17-gauge Tuohy needle was introduced at either the thoracic or lumbar interspace, using the paramedian technique. The extradural space was identified using the loss-of-resistance method with 5 ml of air. When no cerebrospinal fluid or blood flowed from the needle, these patients underwent examination of the lumbar extradural space with a flexible fibrescope measuring 0.7 mm in diameter (Igarashi Ika Kogyo Co., MS-501, Tokyo, Japan) which was connected to a television monitor system (Igarashi Ika Kogyo Co., FV-2000E, Tokyo, Japan). The extraduroscope was introduced approximately 10 cm in a cephalad direction into the extradural space via the Tuohy needle. No air was injected after the insertion of the extraduroscope in each patient. If paraesthesia or resistance were noted during extraduroscope insertion, no attempt was made to advance the extraduroscope through the area of resistance. Consequently, two patients in the lumbar group in whom the extraduroscope could not be advanced more than 5 cm cephalad were excluded from the analysis. Extraduroscopic findings were continuously recorded on a video recorder during the fibrescopic examination in each patient. After the extraduroscopic examination, an extradural catheter (od, 0.85 mm, B. Brown, Bethlehem, PA, USA) was inserted 5 cm in a cephalad direction into the extradural space and the patient was then placed in the supine position. All procedures were performed by the same anaesthetist. The patients received local anaesthetics via the catheter during the planned therapeutic or surgical procedure, with or without general anaesthesia.

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The extraduroscopic findings in our 113 patients were analysed by two independent investigators who did not have access to the patients' medical histories. Furthermore, they were unaware as to whether the extraduroscopy was in the lumbar or thoracic space. The extraduroscopic findings were divided into five categories for analysis: patency of the extradural space after injecting air, amount of fatty tissue, amount of fibrous connective tissue, degree of pulsation and degree of vascularity. The patency of the extradural space was scored using the following grading system: 1=very narrow, 2=patent and 3=widely patent. The other four areas of analysis were scored using the following grading system: 1=none, 2=moderate and 3=considerable. To reach consensus when a discrepancy between two observers in each finding was noted, the difference was resolved by a third experienced investigator. The third investigator was required for 17 patients to give an opinion for the patency of the extradural space, for 20 patients for the amount of fatty tissue, for 25 patients for the amount of fibrous connective tissue, for 15 patients for the degree of pulsation and for 27 patients for the degree of vascularity, all within a total group of 113 patients.

Statistical analyses were carried out using a statistical software package (StatView V4.02, Abacus Concepts, CA, USA) on a personal computer (Macintosh Quadra 650, Apple Computer Inc., CA, USA). Mean (SD) values for age, weight, height, body mass index and body surface area, and median (range) values for each extraduroscopic finding between the lumbar and the thoracic groups were compared using the Mann–Whitney *U* test. A *P* value less than 0.05 was considered statistically significant.

Results

Age, height and weight were comparable between the thoracic and lumbar groups (table 1).

Extraduroscopic examination (fig. 1) revealed that patency of the extradural space after injecting air was greater (P=0.0008), the amount of fatty (P=0.0111) and fibrous connective tissue (P=0.0476) was less and the degree of pulsation was more remarkable (P=0.0002) in the thoracic group than in the lumbar group. No significant differences were detected between the groups in the findings of vascularity.

Figure 2 shows typical findings of the thoracic extradural space. The thoracic extradural space in a 55-yr-old man was observed as a widely patent canal owing to the injected air (fig. 2A). The upper part appeared as a gray membrane and was identified as the dura mater associated with blood vessels, while the lower part of the canal was identified as the ligamentum flavum and the periosteal layer. The few stretched fibrous connective tissues were scattered among the patent canal in the same patient (fig. 2B). Beyond the fibrous connective tissues, fatty tissue was also seen to be thinly spaced.

Figure 3 shows typical findings of the lumbar extradural space. The narrow extradural space made by the injected air was seen in the upper part of the photograph in a 57-yr-old man (fig. 3A). The upper part of the canal that appeared as a grey membrane was identified as the dura mater. The lower part of the photograph appeared as a white membrane and was identified as the periosteal layer. The fibrous connective tissues joined together and formed a membranous structure between the dura mater and the periosteal layer. As the extraduroscope was

Table 1 Patient characteristics. Mean (SD) [range]

	Thoracic group (n=63)	Lumbar group (n=50)	*P*
Age (yr)	60 (10) [41–74]	56 (12) [40–73]	NS
Height (cm)	157 (8) [135–174]	155 (8) [139–170]	NS
Weight (kg)	56 (8) [38–79]	56 (7) [41–75]	NS
Body mass index (kg m^{-2})	23 (3) [18–30]	23 (3) [18–31]	NS
Body surface area (m^2)	1.56 (0.18) [1.26–1.89]	1.53 (0.17) [1.30–1.79]	NS

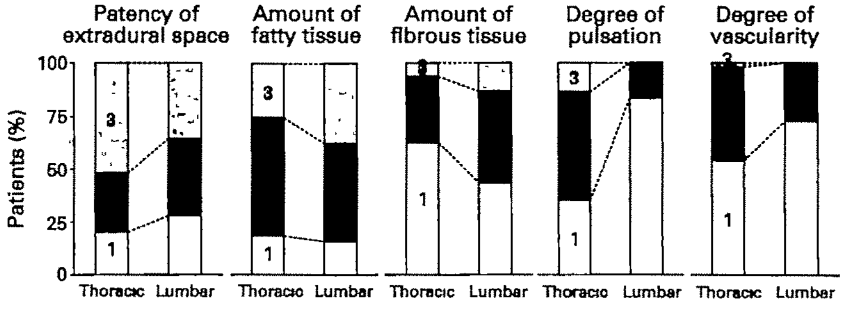

Figure 1 Extraduroscopic findings in the thoracic and lumbar groups. Open bars indicate score 1, solid bars indicate score 2 and shaded bars indicate score 3. Significant differences between the groups were found in the median values for patency of the extradural space after injecting air (P=0.0008), amount of fatty tissue (P=0.0111), amount of fibrous tissue (P=0.0476) and degree of pulsation (P=0.0002). No significant differences between the groups were found with respect to the median values for degree of vascularity.

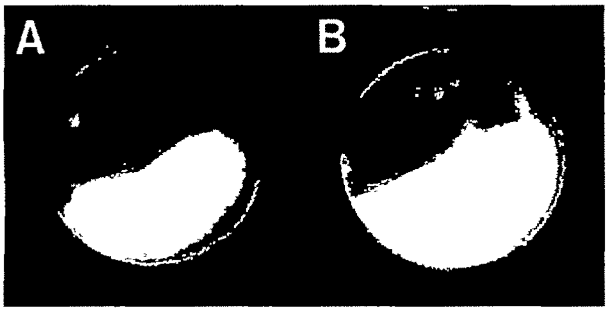

Figure 2 Photographs obtained via the thoracic extraduroscope in a 55-yr-old man. The thoracic extradural space was observed as a widely patent canal owing to the injected air (A). The upper part appeared as a gray membrane and was identified as the dura mater with associated blood vessels, while the lower part of the canal was identified as the ligamentum flavum and the periosteal layer. The few stretched fibrous connective tissues were scattered among the patent canal in the same patient (B). Beyond the fibrous connective tissues, fatty tissue was also seen to be thinly spaced. In this patient, patency of the extradural space after injecting air, amount of fatty tissue, fibrous connective tissue, degree of pulsation and vascularity were scored as 3, 2, 2, 3, and 2 respectively.

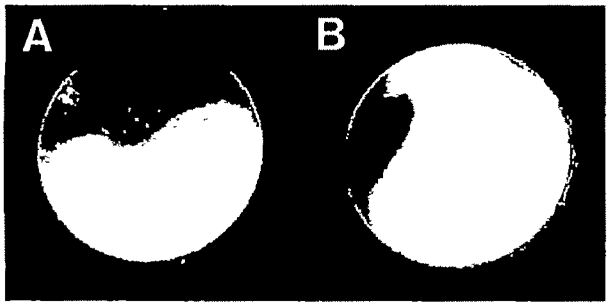

Figure 3 Photographs obtained via the lumbar extraduroscope in a 57-yr-old man. The narrow extradural space made by the injected air was seen in the upper part of the photograph (A). The upper part of the canal that appeared as a gray membrane was identified as the dura mater. The lower part of the photograph appeared as a white membrane and was identified as the periosteal layer. The fibrous connective tissues joined together and formed a membranous structure between the dura mater and the periosteal layer. A large amount of fatty tissue was seen to be under tension and tightly adherent to the dura mater and the periosteal layer as the extraduroscope was advanced (B). The extradural canal appeared to be very short and narrow because of the presence of a large amount of fatty and fibrous connective tissue. In this patient, patency of the extradural space after injecting air, amount of fatty tissue, fibrous connective tissue, degree of pulsation and vascularity were scored as 1, 3, 3, 1, and 2 respectively.

advanced, a large amount of fatty tissue was seen to be under tension and tightly adherent to the dura mater and the periosteal layer (fig. 3B). The extradural space appeared to be very short and narrow because of the presence of a large amount of fatty and fibrous connective tissues.

We encountered no accidental dural punctures and observed no signs of persistent neurological injury in any of our patients.

Discussion

In this study, extraduroscopic examination showed that the patency of extradural space after injecting air was more and the amount of fatty and fibrous connective tissue was less in the thoracic extradural space than in the lumbar extradural space. We suggest that the amount of fatty and fibrous connective tissue in the extradural space may play an important role in determining the patency of the extradural space after injecting air, thereby affecting the longitudinal spread of anaesthetic solution in the different sites of the extradural space.[5 6]

We found that the patency of the extradural space, which was made by 5 ml of air injected into the space, was greater in the thoracic region than in the lumbar region. This difference in the patency of the extradural space after injecting a given amount of air between these two vertebral regions may be influenced by the negative intrapleural and positive intra-abdominal pressures. Because the extradural pressure is lower in the thoracic region than in the lumbar region,[14] thoracic extradural space may be easier to enlarge after the injection of air compared with the lumbar extradural space. In addition, the thoracic vertebral canal is smaller than the lumbar vertebral canal in transverse size.[15] A given amount of air may presumably produce a longer canal in the thoracic extradural space, rather than in the lumbar extradural space. Therefore, the longitudinal spread of local anaesthetics may be related to the findings of the patency of the extradural space after injecting air, as well as the size of the vertebral canal.

In this study, the amount of fatty tissue observed in the extradural space was less in the thoracic than in the lumbar region. The lumbar extradural space is reported to be packed tightly with rigid fat.[16] Because the lumbar vertebrae are able to move by large ranges of flexion, extension and rotation,[17] the large amount of fatty tissue in the lumbar extradural space serves as a cushion for the spinal cord and this may hinder the spread of local anaesthetics. In addition, the amount of fatty tissue in each vertebral region may be a possible reason for the ranges of patency of the extradural space after injecting air. It is reported that a catheter is easily inserted for a longer distance without kinking in the thoracic than in the lumbar extradural space.[18] Increasing amounts of fatty tissue in the lumbar extradural space may simultaneously increase the power of adhesion between fatty tissue and other tissue such as the dura mater and the ligamentum flavum. Therefore, the thoracic extradural space becomes more compliant and less resistant, and patency of the extradural space after injecting air alters according to the vertebral region.

Other connective tissues except for fatty tissue were observed as strands or membranes in the extradural space and we defined them as fibrous connective tissue in this study. These fibrous connective tissues exist among fatty tissue, the dura mater and the periosteal layer, and the amount of fibrous connective tissue revealed a statistically significant difference between thoracic and lumbar extradural space. The fibrous connective tissues joined together and formed a membranous structure in the lumbar extradural space, while in the thoracic extradural space they remained as a strand structure. In some cases, the thin and fragile membrane structures were observed as an incomplete partition in the lumbar extradural space. Along with the amount of fatty tissue, a large amount of fibrous connective tissue in the lumbar extradural space may decrease the longitudinal spread of anaesthetic solution by increasing the power of adhesion among the dura mater, the ligamentum flavum and fatty tissue.

The pulsation of the dural sac may reflect the cerebrospinal fluid pulse wave. The pulse wave is composed of spinal vascular (arterial and venous) pulsation and the intracranial pulse wave transmitted through the spinal canal from the intracranial space to lumbar level.[19] Because the pulse wave of the cerebrospinal fluid is less at lower vertebral levels,[19] the pulsation of the dural sac was more significant in the thoracic than in the lumbar extradural space. A marked pulsation of the thoracic dural sac may, at least in part, support the findings of the great patency of the thoracic extradural space after injecting air because the thoracic dural sac may become more movable by separating from the fatty and the fibrous connective tissues after this injection.

Several factors may have influenced our results. The extradural space was observed after introducing a small amount of air. The extradural space is sometimes described as a potential space, rather than a true cavity.[20,21] The introduction of air might have expanded the extradural space and stretched the connective tissues. However, in our study, all patients received identical extradural punctures and the effects of the air introduced into the extradural space should have been similar in all cases. Therefore, we believe that this factor had no influence on a comparative study.

We found fatty tissue existed like segmental parts in the extradural space as the fibrescope was introduced in a cephalad direction. Sagittal mid-line magnetic resonance imaging[22] and cryomicrotomy[23] have shown that the extradural fatty tissue is divided into segments by the interposing laminae in the lower thoracic and lumbar regions. In this study, extradural structures could be observed mainly from the point where fatty tissue did not exist. Nevertheless the patency of the extradural space after injecting air was similar regardless of whether or not fatty tissue was present.

In this study, thoracic extradural anaesthesia was performed at one point within the Th7–10 interspace, and the extraduroscope was introduced approximately 10 cm in a cephalad direction from the Tuohy needle tip. In the patients of the lumbar group, the tip of the fibrescope could reach the level a little less than Th12 when the extraduroscope was introduced 10 cm in a cephalad direction from the L2–3 interspace. Therefore, we compared anatomical differences between the middle thoracic and upper lumbar extradural space.

In the lower thoracic and lumbar segments, the extradural space has been suggested to be transversely divided into three compartments: anterior, dorsal and dorsolateral.[24,25] The extraduroscope may have advanced through the dorsal compartment into other compartments in the two patients who were excluded from this analysis. Nerve irritations during the extraduroscopic procedures may be closely associated with the fact that the extraduroscope touched the nerve roots after the passage of the extraduroscope through the dorsal compartment into the other compartments. In this study, the tip of the Tuohy needle was introduced into the extradural space as precisely in the midline as possible and no evidence was detected that the extraduroscope advanced into the other compartments in any patients, so the findings were presumably of the dorsal compartment within the extradural space.

Before beginning this study, we considered whether air might be an appropriate injectate in the extradural space. We could not obtain a clear view of the extradural space using the loss-of-resistance method with saline because the saline adhered to the tip of the fibrescope. Therefore, we used air for the loss-of-resistance method and minimized its amount to 5 ml in this study.

The extraduroscopic findings would have had more rigour if some objective measurements, such as a ratio of the object's area to the visible area, had been made. However, because of the characteristics of the magnifying lens, the ratio could change according to the portion of the visible area or the distance between the tip of the fibrescope and the objects. Therefore we opted for semiquantitative analysis with the arbitrary type of scoring rather than precise measurements. To ensure objectivity, the extraduroscopic findings were reviewed by independent investigators who did not have access to the patients' medical histories.

Finally, the patients were classified into two groups according to the site of the extradural anaesthesia as needed for perioperative analgesia. Although we should consider the possibility that non-randomization of the two groups of patients could have influenced the outcome of this study, it is unlikely to have any bearing on the extraduroscopic findings.

In summary, extraduroscopy showed that the thoracic extradural space becomes widely patent after injecting a given amount of air and that the amount of fatty and fibrous connective tissue diminishes in the thoracic extradural space compared with the lumbar extradural space. We suggest that the differences in the structure between these two vertebral regions may affect the spread of local anaesthetics in the extradural space.

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Meta-analysis of the efficacy of extradural clonidine to relieve postoperative pain: an impossible task

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Summary

Clonidine, an alpha$_2$ adrenoceptor agonist, has anti-hypertensive and anti-nociceptive effects. It is commonly used in association with local anaesthetics and opioids to enhance the quality and duration of extradural analgesia in the post-operative period, and to decrease the incidence of side effects. As a sole analgesic, it has seldom been used to relieve postoperative pain. The dose of extradural clonidine to achieve good pain relief without deleterious side effects remains undetermined. In order to address this problem, we performed a computer search via two well-known databases, Medline and Excerpta Medica, covering the period from 1985 to September 1997. One hundred and fifty-nine articles were retrieved of which 38 dealt with extradural clonidine and postoperative pain. All but 16 studies suffered from serious design flaws, such as lack of controls and/or randomization, or inadequate statistical analysis. The data from these studies were difficult to interpret because of the tremendous variation in variables, especially dose of clonidine, level of extradural injection, time of administration, type of anaesthesia, type of surgery, and reference and rescue drugs. The simultaneous extradural use of local anaesthetics and opioids further hindered data interpretation, and precluded any meta-analysis. Proposals for a standard study design are made to help comparison between studies involving extradural clonidine and post-operative pain. (*Br. J. Anaesth.* 1998; **81**: 126–134)

Keywords: analgesic techniques, regional; anaesthetic techniques, extradural; analgesics non-opioid, clonidine; analgesia, postoperative; pain, postoperative

Clonidine, an alpha$_2$ adrenoceptor agonist, is a well-known anti-hypertensive drug. Its antinociceptive properties have been well documented since the early 1970s[1] and widely used since the first report on extradural clonidine in humans by Tamsen and Gordh in 1984.[2] Clonidine appeared devoid of some of the side effects of both local anaesthetics and opioids (that is, motor block, tachyphylaxis, neurological toxicity, respiratory depression, pruritus, and urinary retention) although hypotension, bradycardia and sedation are recognized side effects of clonidine. It is probably used mainly in association with local anaesthetics and/or opioids and via various routes of administration (spinal, intravenous, intramuscular, oral, transdermal, peripheral block)[3–11] in an attempt to decrease the incidence of side effects. Clonidine has less frequently been used alone. As a sole analgesic, at least two areas of controversy remain: the doses required to achieve good pain relief and the extent of side effects.

The aim of our meta-analysis was to assess the efficacy of extradural clonidine in the relief of postoperative pain, to determine whether anti-nociceptive effects and side effects were dose-related, and to what extent the latter were deleterious.

Methods

The literature search aimed to be as comprehensive as possible. The period ranging from 1985 to September 1997 was searched via two widely used computer databases, Medline and Excerpta Medica, using the headings regional analgesia, extradural clonidine, postoperative analgesia, and postoperative pain.

To avoid the risk of overlooking any relevant article, citations from articles were cross-referenced with those of the assessors' bibliography and those of the articles under review. Each study was first reviewed independently by two assessors who filled out a structured form to give a common frame for future discussion (table 1).

Subsequently the assessors collectively classified the articles into 1 of 4 grades according to the type of study design. Grade 1 articles dealt with randomized, controlled, double-blind trials with clearly defined objectives and adequate statistical analysis. Randomized trials lacking control or blinding were classified as grade 2; randomized trials yielding questionable results, or non randomized trials were classified as grade 3, and grade 4 articles consisted of non-randomized or non-controlled trials, case reports, editorials, letters to journal editors, abstracts, and retrospective evaluations. Only articles belonging

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Table 1 Data collection form for meta-analysis

- References: title, first author, review, volume, year, pages, and medical institution
- Main objective of the study
- Type of study: randomized, single or double-blind, controlled, parallel or cross-matched, cohort, and case report
- Population: number of patients, demographic characteristics (age, gender, weight, height, and ASA physical status), homogeneity of the population and statistical tests used, type of surgery, and inclusion and exclusion criteria
- Type of anaesthesia: general, regional or both, type and dose of drugs used, especially opioids, hypnotics, and local anaesthetics
- Postoperative analgesia: clonidine dose and mode of administration (bolus injection and/or continuous infusion), level of extradural injection (lumbar/thoracic), total dose of clonidine; associated analgesics: type, dose, and mode of administration (intravenous, extradural, subcutaneous); and duration of analgesia
- Analgesic efficacy assessment: scales, timing, and results
- Side effects assessment: definition, timing, and severity, with special regard to hypotension, bradycardia, sedation and respiratory depression
- Type of statistical tests and reasoning, number of patients excluded and lost for follow-up.

to the first grade of classification were deemed eligible for meta-analysis.

In order to bring together the different studies, comparisons were made on doses of clonidine, mode of administration (bolus injection or continuous infusion), time of administration, type of anaesthesia and surgery, reference drug, assessment of pain intensity and relief (for example, visual analogue scale, verbal scale), and timing of the assessment. Escape analgesics were also noted.

Results

The search retrieved 159 articles, of which 38 dealt with extradural clonidine, and 16 met the selection criteria.[3,12-26]

The number of patients per group ranged from 20 to 100, with a total of 681 patients. It was not clear in the two studies by Carabine and colleagues[13,14] whether the patients belonged to two different populations.

Clonidine was injected in various ways, bolus injection alone,[12,13,19,24,26] bolus injection followed by continuous infusion,[14,15,21] bolus injection followed by patient-controlled analgesia infusion,[3] bolus injection of a mixed solution followed by a continuous infusion of clonidine, a mixed solution combining clonidine with fentanyl,[16,25] local anaesthetics,[20] or two or more of these drugs[22] and continuous infusion of a mixture of clonidine and morphine [23] (table 2).

Clonidine-bolus doses ranged from 75 μg to 800 μg, and from 1 μg kg^{-1} to 8 μg kg^{-1}, and continuous infusion ranged from 0.3 μg kg^{-1} h^{-1} to 2 μg kg^{-1} h^{-1}, and from 10 μg h^{-1} to 50 μg h^{-1}.

Administration took place either intraoperatively, a few minutes after induction of anæsthesia[15,17]; at the beginning of the surgical procedure,[22] 30 min before the end of the surgical procedure[13,14] or postoperatively, on arrival in the recovery room[16,18,21] 1 h after surgery[26] or at the patients' first complaint of pain.[3,12,16,19,20,24,25]

Side effects were defined in various manners or not defined at all (table 3). The main side effects recorded were hypotension, bradycardia and sedation. Authors often noted that hypotension and bradycardia should they occur were either readily treated (most of the time by an association of ephedrine and volume loading) or necessitated no treatment. When sedation was mentioned, it was not always clear how this was measured. For example, some authors reported only that patients had "marked sedation",[20,21] or that "excessive" sedation was not a problem,[19] or that "sedation was similar in all … groups".[13]

Extradural catheters were inserted either thoracically, or at the high and/or the low lumbar level (table 4).

Pain intensity and relief was assessed by visual analogue score alone, or visual analogue score and verbal scale. The visual analogue scores ranged from 3 to 6 points or were not described. Table 4 also displays when visual analogue scoring was used (only at rest, at rest and at cough, at rest and after mobilization, and at rest, at cough and after mobilization).

Additional analgesics consisted of i.v. patient-controlled analgesia with morphine, pethidine or sufentanil, s.c, i.m. or i.v. morphine, extradural morphine associated with i.v. pethidine, i.v. paracetamol, i.m. piritramide, i.v. ketoprofen, and continuous extradural bupivacaine-fentanyl mixture (table 4).

Clonidine alone at a dose of 3 μg kg^{-1} was found to be as efficacious as placebo in one study after thoracic surgery.[19] In orthopaedic and rectal surgery a lower dose (2 μg kg^{-1}) was found to be more efficacious than placebo.[12] In the remaining studies, the efficacy of clonidine in combination with other drugs was almost always superior to that of each drug alone (table 3).

Discussion

Although our literature search might not have been as comprehensive as it should, it is unlikely that relevant articles were overlooked. Main articles are always published in main journals which are covered by the two selected computer databases, Medline and Excerpta Medica. Moreover, the references of all articles reviewed were also checked. The number of articles dealing with our selection criteria was smaller than expected considering the great number of articles dealing with postoperative pain and clonidine.

Only two dose-response studies were found.[17,27] This type of study should be able to address some of the unresolved problems concerning the efficacy and safety of clonidine.

The most impressive evidence of this review was the lack of at least two study designs enabling direct comparison. We found as many study designs as there were articles. For instance, where bolus doses of clonidine were used, the type of anaesthesia was either general,[13] extradural,[12] or both,[19] and where general anaesthesia alone was used, clonidine was administered by bolus injection,[26] continuous infusion,[23] or both [14] (table 2).

Moreover, when considering only one type of surgery (for example, major abdominal surgery, eight studies) (tables 5, 6 and 7), it was clear that direct comparison between variables was not possible.

The most serious shortcoming of all published studies dealing with postoperative extradural clonidine was the lack of a common background. Consequently, meta-analysis could not be applied to the selected trials.

Table 2 Main data from 16 randomized double-blind studies dealing with extradural clonidine and postoperative pain. *n**=total number of patients; PCA=patient-controlled analgesia; PCEA=patient-controlled-extradural analgesia; Cont. infus.=continuous infusion; EA=extradural anaesthesia; GA=general anaesthesia; i.v.=intravenous; ED=extradural; CL=clonidine; F=fentanyl; M=morphine; B=bupivacaine; THR=total hip replacement; *=9 patients not responding to the study drug within 60 min postoperatively were excluded; †=in parentheses, total number of patients left during the postoperative period after 13 patients had been excluded intraoperatively because of inadequate anaesthesia

Year	Authors	*n**	Dose of clonidine	Mode of administration	Time of administration	Reference drug	Duration of study (h)	Type of anaesthesia	Type of surgery
1988	Gordh	20	3 µg kg^{-1}	Bolus injection	1st request	Placebo	12	EA + GA	Thoracotomy
1989	Bonnet	20	2 µg kg^{-1}	Bolus injection	1st request	Placebo	6	EA and/or GA	Orthopaedic and rectal
1990	Motsch	91	450 µg in 24h	Contin. infus. CL + M	1st request	Morphine	72	GA	Abdominal
1990	Mendez	60	400 µg + 10 µg h^{-1} 800 µg + 20 µg h^{-1}	Bolus inj. + Cont. Infus.	Recovery room	Placebo	24	EA	C-section
1991	Rostaing	20	150 µg CL + 100 µg F	Bolus inj. CL + F	1st request	Fentanyl	12	EA + GA	Abdominal aorta
1991	Van Essen	28	75 µg	Bolus injection	1h after surgery	Morphine	6	GA	Menisectomy
1992	Carabine	90	150 µg	Bolus inj.	Intraoperativ.	Bupivacaine	12	GA	THR
1992	Carabine	100	150 µg + 25 µg h^{-1} 150 µg + 50 µg h^{-1}	Bolus inj. + Cont. infus.	Intraoperativ.	Morphine	24	GA	THR
1992	Huntoon	60	400 µg + 40 µg h^{-1} 800 µg + 40 µg h^{-1}	Bolus inj. + Cont. infus.	1st request	Placebo	24	EA	C-Section
1992	Mogensen	22	75 µg + 18.75 µg^{-1} h^{-1} + B + M	Bolus inj. + Cont. infus.	Intraoperativ.	B + M + Saline	12	EA + GA	Abdominal hysterectomy
1993	De Koch	40	4 µg kg^{-1} + 2 µg kg^{-1} h^{-1}	Bolus inject. + Cont. infus	Intraoperativ. and postoperativ.	i.v. CL	36	GA	Abdominal
1993	Delaunay	25	0.3 µg kg^{-1} h^{-1} + Fentanyl	Contin. infus. CL + F	Recovery room	Fentanyl	72	EA + GA	Colorectal
1995	Bernard	24	8 µg kg^{-1} + 30 µg/15 min	Bolus injection + PCEA	1st request	i.v. CL + i.v. PCA CL	10	GA	Scoliosis repair
1995	De Koch	40	4 µg kg^{-1} + 2 µg kg^{-1} h^{-1}	Bolus injection + Cont. Infus.	1st request	ED sufentanil	12	GA	Intestinal resection or reanastomosis
1995	Rockemann	45*	8 µg kg^{-1} 4 µg kg^{-1} + M	Bolus injection	1st request	Morphine	10	EA + GA	Pancreatic
1997	De Koch	50	2 µg kg^{-1} + 0.5 µg kg^{-1} h^{-1}	Bolus injection + Cont. infus.	Intraoperativ. and postoperativ.	/	12	GA	Abdominal
		(36)†	4 µg kg^{-1} + 1 µg kg^{-1} h^{-1} 8 µg kg^{-1} + 2 µg kg^{-1} h^{-1}						

Table 3 Main side-effects and analgesic variables from 16 randomized double-blind studies dealing with extradural CL and postoperative pain. *=Analgesic duration of CL alone, in min, values are mean (SD); †=analgesic efficacy variously evaluated (VAS score and/or verbal score and/or total consumption of supplemental analgesics or percent reduction in pain); +: presence of data, –. absence of data; NM=not mentioned and/or no definition of the side-effect available; CL=clonidine; M=morphine; F=fentanyl, Suf=sufentanil; Pl=placebo; B=bupivacaine; Chl=chloroprocaine; ED=extradural; i.v.=intravenous; [a]=time from when PCA was connected (30 min after CL injection) to the first self-administered dose; [b]=values are means ± SEM; [c]=time from CL injection to first use of supplemental morphine in the bupivacaine group; [d]=time from CL injection to first use of supplemental morphine in the chloroprocaine group; [e]=no definition of hypotension; [f]=no definition of bradycardia; [g]=time from tracheal extubation to first analgesic demand in the extradural group, [h]=time from tracheal extubation to first analgesic demand in the intravenous group; [i]=less morphine requirements in the ED CL group, but same VAS scores; [j]=same VAS scores between groups, but PCEA dose less than IV dose of CL; [k]=time from extubation to first analgesic demand; [l]=reduction in heart rate, no definition of bradycardia available

					Treatment of				
Year	Authors	Sedation	Hypotension	Bradycardia	Sedation	Hypotension	Bradycardia	Duration of analgesia*	Analgesic efficacy of clonidine†
1988	Gordh	-	+	-	-	-	-	11.3 (12.55)[a]	CL=Pl
1989	Bonnet	Drowsiness	+	-	-	-	-	210 (87)	CL>Pl
1990	Motsch	CL+M=M	+	+	-	+	-	NM	CL+M>M
1990	Mendez	+ dose-dependent	+	+	-	-	+	270 (400 μg CL) 300 (800 μg CL)	CL800 μg>400 μg>Pl
1991	Rostaing	+	+	+	NM	+	NM	543 (183)[b]	CL+F>F
1991	Van Essen	-	+	NM	-	NM	NM	NM	CL+M=M>CL
1992	Carabine	+	+ CL=B=CL+B	-	-	+	-	179 (17)[b]	CL=CL+B>B
1992	Carabine	-	+	-	-	-	-	144 (99) 286 (112)	50 μg>25 μgCL=M+CL>M
1992	Huntoon	+ dose-dependent	+	+	-	+	-	210 (400 μg CL)[c] 330 (800 μg CL)[c] 30 (400 μg CL)[d] 48 (800 μg CL)[d]	B+800 μg CL>B+400 μg CL >Chl+800 or 400 μg CL
1992	Mogensen	NM	+	NM	NM	+	NM	NM	CL+B+M>B+M
1993	De Koch	+	-[e]	-[f]	-	-	-	103 (115)[g] 83 (106)[h]	ED>i.v. CL[i]
1993	Delaunay	F+CL=CL	+	-	-	+	-	NM	F+CL>F
1995	Bernard	+	+	-	-	+	-	NM	ED>i.v. CL[j]
1995	De Koch	+	+	-	-	-	-	321 (332)[k]	ED CL=ED Suf (6 first h), ED CL>ED Suf (beyond 6th h)
1995	Rockemann	NM	+	-[l]	NM	-	NM	33.6 (118) (CL) 585 (217) (CL+M)	M>CL+M>CL
1997	De Koch	+ not dose-dependent	-	-	-	-	-	30 (21) (low-dose) 251 (237) (medium-dose) 369 (256) (high-dose)	High>medium>low-dose CL

Table 4 Main characteristics of study design of 16 randomized double-blind studies dealing with extradural clonidine and postoperative pain. LA*=local anaesthetic; †=heart rate (bpm); ED=extradural; EA=extradural anaesthesia; GA=general anaesthesia; NM=not mentioned; [#]=extradural catheter was inserted 1 h after surgery; i.v. PCA=intravenous patient-controlled analgesia; i.m.=intramuscular; cont. inf.=continuous infusion; VS=verbal scale: VAS=visual analogue scale; Epineph=epinephrine; B=bupivacaine; Priloc=prilocaine; F=fentanyl; M=morphine; MAP=mean arterial pressure, SAP=systolic arterial pressure; [a]=it is not clear whether pain was evaluated at rest, motion or during cough; [b]=no patients received opioids during GA; [c]=lidocaine concentration not mentioned; [d]=study results are in mean (SEM); [e]=study results are in mean (SD); [f]=study results are in median values and ranges

Year	Authors	Level of ED catheter	Test dose for EA: LA*/ volume	Local anaesthetic used for EA: Type/ volume	Maintenance of GA (drugs)	Sedation scale (degrees)	Evaluation of pain: how/ when	Definition of Hypotension	Definition of Bradycardia†	Rescue drug
1988	Gordh	T4	2% priloc + epineph / 4ml	2% prilocaine / 3–6 ml	F + enflurane	6	Pethid consumption / NM[a]	<100 mm Hg(?)	NM	i.v. PCA pethidine
1989	Bonnet	Lumbar	NM	2% lidocaine NM	NM[b]	NM	VAS formula NM	NM	NM	5 mg s c./M
1990	Motsch	L1-2 or L2-3	0.5% plain B / 4 ml	0	F + isoflurane	4	Analgesic consumption + VAS / NM	↘ ≥30% MAP or SAP	NM	ED 2 mg M, then i v. pethid
1990	Mendez	L3-4 or L4-5	2% lidocaine / 2 + 5 ml	0.5% B / <50 ml	0	5	5-point VS / NM	↘ ≥30% AP	<50	i.v. PCA M
1991	Rostaing	T12-L1 or L1-2	NM	0.5% B / NM	F (for intubation) then isoflurane	NM	VAS formula / NM	↘ ≥25% MAP or SAP<90 mm Hg	<50	i v. paracetamol
1991	Van Essen	L2-3[#] / 2 ml	Lidoc[c] + Epineph	0	≤2% halothane, no opioids	NM	VAS / NM	NM	NM	i.m. piritramide
1992	Carabine[d]	L1-2 or L2-3	1.5% plain lidocaine / 3 ml	0	1–1.5% isoflurane, no opioids	3	VAS / NM	SAP<85 mm Hg and ↘ MAP (?)	<45	0.1 mg h^{-1} ED M ± i.v. M + i.m. M
1992	Carabine[e]	L1-2 or L2-3	1.5% plain lidocaine / 3 ml	0	1–1.5% isoflurane, no opioids	3	4-point VS+VAS + total i.v. M / NM	SAP<85 mm Hg and ↘ MAP (?)	<45	i.v. PCA M
1992	Huntoon	L3-4 or L4-5	2% lidoc / 2+5 ml or 3% 2-Chl / 2+5 ml	3% 2-Chl or 0.5% B / <50 ml	0	5	5-point VS / NM	↘ ≥30% MAP	<50	i.v. PCA M
1992	Mogensen[f]	T10–11	0.5% plain B / 3 ml	0.5% B 5ml+1mg M, + cont. inf. (0.125%B+M)	Isoflurane, no opioids	NM	5-point VS + VAS / rest, cough, mobilization	SAP<80 mm Hg	NM	i.m. M
1993	De Koch	L1-2	0	0	Propofol infusion ± alfentanil	4	4-point VS + VAS rest, mobilization	NM	NM	i.v. PCA M
1993	Delaunay	Lower thoracic	NM	2% lidoc.+0.5% B as required	Isoflurane	4	VAS	SAP<90 mm Hg	<45	i.v. paracetamol
1995	Bernard	Caudal route, tip at lumbar level	0 (radio control)	0	Isoflurane	5	VAS / NM	MAP<55 mm Hg	<45	i.v. ketoprofen
1995	De Koch	L1-2	NM	0	Propofol infusion ± sufentanil	3	VAS / rest, mobilization	↘ ≥30% AP	NM	i.v. PCA Suf.
1995	Rockemann	T7–10 day before surgery	1% mepivacaine / 5 ml	0.25% B / 10–15 ml	Enflurane	3	VAS / rest	NM	NM	ED 0.25% B + F
1997	De Koch	T8-9	0	0 / 2 ml	Propofol infusion ± bolus propofol ± i.v. bolus lidocaine 1 mg kg^{-1} ± opioids	4	VAS / rest, cough	↘ ≥30% SAP	<40	ED 0 125% B

Table 5 Some variables from eight randomized double-blind studies dealing with extradural clonidine to relieve postoperative pain after major abdominal surgery. n*=total number of patients; CL=clonidine; F=fentanyl; M=morphine; B=bupivacaine; Contin. infus.=continuous infusion; ED=extradural; EA=extradural anaesthesia; GA=general anaesthesia; i.v.=intravenous, Intraoperativ.. clonidine administered at the beginning of the procedure; *=nine patients not responding to the study drug within 60 min postoperatively were excluded; †=in parentheses, the total number of patients left during the postoperative period after 13 patients had been excluded intraoperatively because of inadequate anaesthesia

Year	Authors	n*	Dose of clonidine	Mode of administration	Time of administration	Reference drug	Duration of study (h)	Type of anaesthesia	Type of surgery
1990	Motsch	91	450 μg / 24 h	Contin. infus. CL + M	1st request	Morphine	72	GA	Abdominal
1991	Rostaing	20	150 μg CL +100 μg F	Bolus inj. CL + F	1st request	Fentanyl	12	EA + GA	Abdominal aorta
1992	Mogensen	22	75 μg +18.75 μg^{-1} h^{-1} + B + M	Bolus inj. + Contin. infus.	Intraoperativ.	B + M + Saline	12	EA + GA	Abdominal hysterectomy
1993	De Koch	40	4 μg kg^{-1} + 2 μg kg^{-1} h^{-1}	Bolus inject. + Contin. infus.	Intraoperativ. and postoperativ.	i.v. CL	36	GA	Abdominal
1993	Delaunay	25	0.3 μg kg^{-1} h^{-1} + Fentanyl	Contin. infus. CL + F	Recovery room	Fentanyl	72	EA + GA	Colorectal
1995	De Koch	40	4 μg kg^{-1} + 2 μg kg^{-1} h^{-1}	Bolus injection + Contin. infus	1st request	ED sufentanil	12	GA	Intestinal resection or reanastomosis
1995	Rockemann	45*	8 μg kg^{-1} 4 μg kg^{-1} + M	Bolus injection	1st request	Morphine	10	EA + GA	Pancreatic
1997	De Koch	50 (36)†	2 μg kg^{-1}+0.5 μg kg^{-1} h^{-1} 4 μg kg–1 +1 μg kg–1 h–1 8 μg kg^{-1}+2 μg kg^{-1} h^{-1}	Bolus injection + Contin. infus.	Intraoperativ. and postoperativ.	/	12	GA	Abdominal

Table 6 Some variables from eight randomized double-blind studies dealing with extradural clonidine to relieve postoperative pain after major abdominal surgery. *=Values are in minutes and mean (SD), †=analgesic efficacy variously evaluated (VAS score and/or verbal score and/or total consumption of supplemental analgesics or percent reduction in pain); +· presence of data; -. absence of data; NM=not mentioned and/or no definition of side effect available, CL=clonidine; B=bupivacaine; M=morphine; F=fentanyl, Suf=sufentanil; Pl=placebo, ED=extradural; i.v.=intravenous; ^{a}=values are means (SEM); ^{b}=no definition available; ^{c}=time from tracheal extubation to first analgesic demand in the extradural group; ^{d}=time from tracheal extubation to first analgesic demand in the i.v. group; ^{e}=less morphine requirements in the ED CL group, but same VAS scores; ^{f}=time from extubation to first analgesic demand; ^{g}=reduction in heart rate, no definition of bradycardia available

					Treatment of				
Year	Authors	Sedation	Hypotension	Bradycardia	Sedation	Hypotension	Bradycardia	Duration of analgesia*	Analgesic efficacy of clonidine†
1990	Motsch	CL+M=M	+	+	-	+	-	NM	CL+M>M
1991	Rostaing	+	+	+	NM	+	NM	543 (183)^{a}	CL+F>F
1992	Mogensen	NM	+	NM	NM	+	NM	NM	CL+B+M>B+M
1993	De Koch	+	-^{b}	-^{b}	-	-	-	103 (115)^{c} 83 (106)^{d}	ED>IV Cl^{e}
1993	Delaunay	F+CL=CL	+	-	-	+	-	NM	F+CL>F
1995	De Koch	+	+	-	-	-	-	321 (332)^{f}	ED CL=ED Suf (6 first h), ED CL>ED Suf (beyond 6th h)
1995	Rockemann	NM	+	-^{g}	NM	-	NM	336 (118) (CL) 585 (217) (CL+M)	M>CL+M>CL
1997	De Koch	+ not dose-dependent	-	-	-	-	-	30 (21) (low-dose) 251 (237) (medium-dose) 369 (256) (high-dose)	High>medium>low-dose CL

Table 7 Some variables from eight randomized double-blind studies dealing with extradural clonidine to relieve postoperative pain after major abdominal surgery. LA*=local anaesthetic; †=heart rate (bpm); NM=not mentioned; ED=extradural; EA=extradural anaesthesia; GA=general anaesthesia; B=bupivacaine; F=fentanyl; M=morphine; Suf=sufentanil; Pethid.=pethidine; i.v. PCA=intravenous patient-controlled analgesia; i.m.=intramuscular; Cont. inf =continuous infusion; VS=verbal scale; VAS=visual analogue scale; MAP=mean arterial pressure; SAP=systolic arterial pressure

Year	Authors	Level of ED catheter	Test dose for EA: LA*/ volume	Local anaesthetic used for EA: Type / volume	Maintenance of GA (drugs)	Sedation scale (degrees)	Evaluation of pain how/when	Definition of Hypotension	Definition of Bradycardia†	Rescue drug
1990	Motsch	L1-2 or L2-3	0.5% plain B / 4 ml	0	F + isoflurane	4	Analgesic consumption +VAS / NM	↘ ≥30% MAP or SAP	NM	ED 2 mg M, then i.v. pethid
1991	Rostaing	T12-L1 or L1-2	NM	0.5% B / NM	F (for intubation) then isoflurane	NM	VAS formula / NM	↘ ≥25% MAP or SAP <90 mm Hg	<50	i.v. paracetamol
1992	Mogensen	T10–11	0.5% plain B / 3 ml	0.5% B 5 ml + 1mg M, + cont. infus. of 0.125%B with M	Isoflurane, no opioids	NM	5-point VS+VAS / rest, cough, mobilization	SAP<80 mm Hg	NM	i.m. M
1993	De Koch	L1-2	0	0	Propofol infusion ± alfentanil	4	4-point VS + VAS / rest, mobilization	NM	NM	i.v. PCA M
1993	Delaunay	Lower thoracic	NM	2% lidoc. + 0.5% B / "as required"	Isoflurane	4	VAS / NM	SAP<90 mm Hg	<45	i.v. paracetamol
1995	De Koch	L1-2	NM	0	Propofol infusion ± sufentanil	3	VAS / rest, mobilization	↘ ≥30% AP	NM	i.v. PCA Suf.
1995	Rockemann	T7–10 day before surgery	1% mepivacaine / 5 ml	0.25% B / 10–15 ml	Enflurane	3	VAS / rest	NM	NM	ED 0.25% B + F
1997	De Koch	T8-9 / 2 ml	0	0	Propofol infusion ± bolus propofol ± i.v. bolus lidoc. 1mg kg^{-1} ± opioids	4	VAS / rest, cough	↘ ≥30% SAP	<40	ED 0.125% B

Meta-analysis has increased in popularity during the past 10 years, along with literature reviews. Unlike the latter, which is a qualitative analysis, the former is a quantitative analysis of data from multiple clinical trials,[28-30] " a systematic reviewing strategy for addressing research questions that is specially useful when results from several studies disagree with regard to magnitude or direction of effect."[31]

Controversy exists regarding the way to perform meta-analysis. Some assume that all available data should be taken into account, including unpublished data, abstracts, case reports, and personal data, because published data may favour positive results. Others would select only well-designed randomized controlled trials.[32,33]

However, the need for well-designed controlled trials to assess the analgesic efficacy of clonidine has been emphasized in a recent editorial.[34] The author stated that clonidine alone was ineffective and should not be used as a sole analgesic agent for postoperative or chronic pain, and as the occurrence of side effects was unavoidable and dose-related, high doses of clonidine should not be used. Surprisingly, the author backed up this statement with data from two studies involving a small number of patients (n=10) and small doses of clonidine (150 μg).[4,35] Moreover, cross-over studies, such as these, may have many shortcomings, and are not considered as a "gold standard" for clinical trials. There are well-designed studies from which the author could have assumed, for example,that a dose of clonidine of 150 μg or less is constantly ineffective whatever the type of surgery,[12,19] or if there is some evidence that so small a dose can be effective it may be because of in part the concomitant administration of other analgesic drugs such as local anaesthetics and/or opioids,[26] or to other variables such as the probable effect of benzodiazepines used for premedication.

Premedication also varied greatly from one study to another. The drugs used were diazepam 10 mg orally 1 h before the procedure[19]; diazepam 0.2 mg kg^{-1} with time and route of administration unknown[22]; oral flunitrazepam 1 mg time unknown[12]; 0.75 mg kg^{-1} meperidine and 0.5 mg i.m. atropine 45 min before[23]; 0.5 mg i.m. atropine 30 min before[26]; temazepam 20 mg 60–90 min before[13,14]; lormetazepam 2 mg sublingually the night and 1 h before the procedure[15-17]; flunitrazepam 1 mg or hydroxyzine 100 mg orally 90 min before,[18] and no premedication.[3,20,21,24,25]

Researchers should be encouraged to perform randomized dose-response placebo-control studies, involving many patients in order to increase the power. Authors should take into account previous published analgesic regimens, avoid references such as abstracts,[21,23,25] and adopt rigorous exclusion criteria (no pretreatment involving clonidine or any other antihypertensive drug, benzodiazepines, tricyclic antidepressants, or non-steroidal drugs), as well as rigorous inclusion criteria (patients aged 18–75 years, ASA I or II, probably more than 40–50 patients per group) and a strict study design.

In conclusion, despite the frequent use of clonidine perioperatively, the dose requirements to provide effective analgesia after a surgical procedure remains a matter of personal choice. A meta-analysis of the numerous articles dealing with extradural clonidine and postoperative pain could not be carried out because of the tremendous variety of the study designs. The need for well-designed randomized dose-response controlled studies based on previous studies is clear, so that an optimal extradural clonidine dose regimen can be determined for postoperative pain relief. Side effects should be strictly defined, and their occurrence clearly reported. In addition, patient satisfaction should be evaluated.

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Intrathecal diamorphine compared with morphine for postoperative analgesia after Caesarean section under spinal anaesthesia

S. W. HUSAINI AND I. F. RUSSELL

Summary

A randomized, double-blind study of 40 women was performed to compare patient controlled anaesthesia (PCA) morphine requirements after spinal anaesthesia for elective Caesarean section. The women received 0.2 mg of either morphine or diamorphine mixed with 0.5% bupivacaine in 8% dextrose. There were no significant differences between the groups in terms of VAS for pain, either while supine or trying to turn over. The median VAS for itching were significantly higher in the morphine group at 3, 4, 6, 8 and 12 h. Similarly, the VAS for drowsiness were significantly higher in the morphine group at 6 and 8 h. Overall there was no difference in the 24-h PCA morphine demands between the two groups (diamorphine patients 5.5 mg, morphine patients 5.0 mg. (*Br. J. Anaesth.* 1998; **81**: 135–139)

Keywords: analgesia, postoperative; analgesics opioid, diamorphine; analgesics opioid, morphine; surgery, obstetrical

Intrathecal opioids make a considerable contribution to postoperative analgesia and are frequently used as part of a spinal anaesthetic technique. A recent 17 nation European survey revealed that as many as 12 opioids are used intrathecally for postoperative pain relief.[1] In all countries except the United Kingdom morphine was the most commonly used of the longer acting intrathecal opioids, indeed in 13 countries morphine was the most commonly used opioid.[1] In the UK, diamorphine was the most commonly used opioid with morphine relegated to third place after fentanyl.[1]

As regards intrathecal use, the higher lipid solubility of diamorphine compared with morphine (octanol-water coefficient 280 *vs* 1.4) is believed to confer certain advantages. There is a shorter latency of onset because of its more rapid uptake into neural tissues and this rapid uptake leads to a shorter half-life in the CSF which is thought to lower the risk of centrally mediated side effects (for example, respiratory depression, itching, urinary retention).[2 3]

Compared with a saline placebo intrathecal diamorphine significantly reduces postoperative patient controlled analgesia (PCA) morphine requirements after Caesarean section.[4] However, in this study[4] 68% of the diamorphine group required postoperative opioids. This contrasts with several recent investigations that have shown no requirement for postoperative opioid analgesia after intrathecal morphine for Caesarean section.[5-9] It would appear from a comparison of these publications [5-9] with our findings[4] that morphine may have a significant advantage in terms of reduced postoperative opioid requirements after Caesarean section. There are few data available comparing morphine with diamorphine.[10] Therefore, we designed this study to make a direct comparison of the efficacy of morphine and diamorphine in reducing postoperative opioid requirements after spinal anaesthesia for elective Caesarean section.

Method

The investigation was approved by the local Medical Ethics Committee. After discussion of the study aims, the use of rectal diclofenac, PCA and the use of visual analogue scores (VAS), informed consent was obtained from 40 patients presenting for elective Caesarean section. After obtaining written consent we randomly allocated the patients by means of a sealed envelope to the diamorphine or morphine group. All patients received oral ranitidine 150 mg the evening before and morning of their surgery, with 30 ml 0.3 mol litre^{-1} sodium citrate orally immediately before walking to the operating theatre.

After establishing i.v. access with a 16-gauge cannula, each patient was placed in the right lateral position and baseline arterial pressure was noted. No preload was given. A 25-gauge pencil point spinal needle was inserted at either the L3/4 or L2/3 interspace. After obtaining free flow of CSF, the intrathecal injection was made with the needle orifice facing cranially. CSF was aspirated once during the injection procedure and again at the end of the injection to ensure constant needle position. Patients received a dose of 0.5% heavy bupivacaine between 2.0 and 2.8 ml. In addition, the diamorphine group (group D) received diamorphine 0.2 mg dissolved in 0.2 ml normal saline, and the morphine group (group M) preservative free morphine 0.2 mg in 0.2 ml (morphine sulphate, 1 mg ml^{-1} isotonic injection, Huddersfield Royal Infirmary Pharmacy Manufacturing Unit).

The opioid solutions were prepared by a separate person immediately before the spinal anaesthesia was performed and were presented to the anaesthetist in a 2.0-ml syringe labelled with the trial number; using

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a 1.0-ml syringe 0.2 ml of this solution was added to the appropriate volume of bupivacaine by the anaesthetist (SH or IFR) who was unaware of which solution was being used.

Immediately on completion of the spinal injection, an infusion of Ringer's solution containing ephedrine 60 mg litre^{-1} was infused and the rate was titrated according to the systolic pressure. The patient was turned supine and the table was tilted to the right hip up position. Arterial pressure and pulse rate were measured by an automatic non-invasive monitor at least once a minute until stable and a paper record was printed automatically. If the systolic pressure began to fall the ephedrine infusion rate was increased and if this was not effective in halting the decline in arterial pressure by the time of the next arterial pressure determination additional increments of ephedrine (6 mg) were given as required. Nausea and vomiting were treated by i.v. metoclopramide (10 mg) and ephedrine (6 mg) as indicated.

The level of anaesthesia was assessed by touch with a blunt pin (Neurotip, Owen Mumford Ltd, Brook Hill, Woodstock, Oxford, OX20 1TU) at 2, 5, 10, 15, 20, 30, and 60 min, and thereafter every hour postoperatively until discrimination to touch had regressed to below the inguinal ligament. Anaesthesia was considered adequate for surgery if touch sensation was lost at the T5 level. Intraoperatively, the level of block was assessed as described above and patient discomfort was elicited by direct questioning.

Oxygen (4 litre min^{-1}) was administered via a Hudson mask until delivery, at which time oxytocin 5 units was given i.v. as the cord was clamped. Apgar scores were assessed at 1 min and 5 min. At the end of surgery all patients received cyclizine 50 mg i.m. and rectal diclofenac sodium 75 mg. In accordance with our hospital practice the urinary catheter was left *in situ* and removed some 24 h after surgery.

VAS for pain, sedation, and itch were obtained at the end of surgery and then at 2, 3, 4, 6, 8, 12, 24 and 48 h from the time of spinal injection. At each time interval, a new sheet with four 100-mm VAS lines was used. The ends of the VAS lines were marked as follows: "no pain" and "worst possible pain"; "wide awake and alert" and "very, very sleepy"; "no itching" and "worst possible itching". There were two separate VAS lines for pain: while resting and while attempting to turn over.

Immediately after surgery, patients returned to a four-bedded room on the post-natal ward where a Graseby PCA system was attached to a valved Y connector in the infusion catheter close to the cannula. The system delivered an on-demand bolus of morphine 1 mg with a lock-out time of 3 min and no background infusion. The patients were under constant visual observation by a midwife and, in addition, the midwifery staff recorded a sedation score and respiratory rate on an hourly basis. Rectal diclofenac (75 mg) was prescribed to be given routinely night and morning and in addition paracetamol 1000 mg with codeine phosphate 60 mg (Kapake), chlorpheniramine 4 mg orally or 10 mg i.m. and cyclizine 50 mg i.m. were all prescribed on a patient demand basis.

Based on the difference between our observations[4] and those of others[5-9] a sample size of 20 patients per group was estimated for a 90% power of detecting a difference of 18 mg in postoperative opioid analgesia requirements at the 0.5% level.

The statistical tests were performed using the Statistical Package for the Social Sciences (SPSS, version 7.51) but 95% confidence intervals for the difference between medians were calculated with a macro running in Excel (version 7.0) based on the method described by Campbell and Gardiner.[11] The chi-square test and, where appropriate, Fisher's exact test, were used to analyse the incidence of intraoperative and postoperative sequaelae. Because of the skewed data the Mann–Whitney U test was used to analyse postoperative PCA morphine requirements and VAS. The t test was used for analysis of patient characteristics and infant data. A P value of < 0.05 was considered to be statistically significant.

Results

The groups were comparable in terms of patient characteristics, gestation, duration of surgery, uterine incision to delivery interval (U-D), volume of fluid used and the amount of ephedrine (table 1).

The number of women with intraoperative side effects was similar in the two groups (table 2). Episodes of hypotension were short-lived (< 60–120 s) and, apart from the ephedrine infusion, no patient required additional increments of ephedrine. Intraoperative nausea was also very short-lived and the use of metoclopramide was similar in each group.

There was no difference in the speed of onset, maximum height or duration of the block between the two groups (table 2). Both groups attained a median level of anaesthesia to T3 within 10 min. After 2 h the number of patients with remaining levels of anaesthesia was insufficient to allow meaningful statistical analysis. No patient experienced

Table 1 Patient characteristics and intraoperative details. Mean (SD) (No significant differences.) U–D interval = uterine incision to delivery interval

	Group D (n = 20)	Group M (n = 20)
Age (yr)	31 (3.4)	30 (4.3)
Height (cm)	162 (5.6)	165 (6.3)
Weight (kg)	67.3 (13.8)	69 9 (15.4)
Gestation (wk)	39 (1)	39 (1)
Duration of surgery (min)	50.6 (7.5)	55.9 (12.1)
U–D interval (s)	69 (34)	70 (31)
Ringer's solution used pre-delivery (ml)	872 (160)	851 (193)
Ephedrine used (mg)	52 (9.6)	51 (11.5)

Table 2 Number of patients with specific intraoperative side effects. Height of block is the median dermatomal level (upper quartile, lower quartile). (No significant differences)

	Group D (n = 20)	Group M (n = 20)
Nausea (n)	13	14
Metoclopramide use (n)	5	7
Vomiting (n)	1	0
Headache (n)	2	3
Maximum height of block	T3 (T4,T2)	T3 (T4,T2)
Height of block at 2 h	T10 (T10,T8)	T10 (L1,T8)
> 30% fall in blood pressure (n)	6	7
Supplementary analgesia (n)	0	0
Aware of mild pulling sensation (n)	12	16

Table 3 Number of patients using ancillary drugs in first 24 hours. (No significant differences.) *One diamorphine patient received both additional metoclopramide and prochlorperazine. One morphine patient received additional cyclizine, metoclopramide and ondansetron. † One diamorphine and one morphine patient received oral medication on two occasions One diamorphine and one morphine patient received a single dose of i.v. therapy and another morphine patient required i.v. therapy on two occasions. ‡ One morphine patient did not receive any diclofenac. She used 19 mg PCA morphine in total—15 mg in first 4 h

	Group D	Group M
Anit-emetic*	4	6
Anti-itch†	2	6
Kapake	3	6
Diclofenac‡ (150 mg)	12	10
Diclofenac‡ (75 mg)	8	9

Table 4 PCA morphine use (mg) in the various time epochs. Median dose (lower quartile, upper quartile). 95% confidence intervals (CI) for the difference between the medians (mg). (No significant differences)

Time epoch	Group D	Group M	95% CI
1–4	1.5 (0, 2.8)	2.5 (0, 7.3)	0 to 3
5–8	1.0 (0, 2.8)	1.0 (0, 4.0)	–1 to 1
9–12	0 (0, 3.5)	0 (0, 1.8)	–1 to 0
13–24	0 (0, 5.6)	0 (0, 11.5)	0 to 2
Total	5.5 (1.3, 14.3)	5.0 (2.3, 27.3)	–3 to 10

Table 5 VAS scores for sedation (mm) Median (lower quartile, upper quartile), significance value (*P* value) of difference, and 95% confidence intervals (CI) for the difference in the medians (mm)

Time epoch	Group D	Group M	Significance (*P*)	95% CI
End of surgery	30 (3, 45)	30 (0, 45)	ns	–20 to 50
2 h	40 (3, 70)	38 (20, 61)	ns	–20 to 20
3 h	40 (20, 70)	30 (10, 50)	ns	–30 to 10
4 h	45 (6, 74)	45 (10, 70)	ns	–15 to 20
6 h	25 (0, 50)	60 (25, 80)	0.05	0 to 40
8 h	10 (0, 49)	50 (33, 84)	0.01	10 to 50
12 h	38 (0, 70)	70 (50, 80)	0.06	0 to 50
24 h	10 (0, 29)	20 (1, 50)	ns	–5 to 30

Table 6 VAS scores for itch (mm). Median (lower quartile, upper quartile), significance (*P* value) of difference, and 95% confidence intervals (CI) for the difference in the medians (mm)

Time epoch	Group D	Group M	Significance (*P*)	95% CI
End of surgery	0 (0, 0)	0 (0, 0)	ns	0 to 0
2 h	10 (0, 28)	30 (0, 55)	ns	0 to 30
3h	25 (0,44)	40 (25, 60)	0.03	0 to 30
4 h	20 (0, 38)	50 (31, 60)	0.003	10 to 40
6 h	10 (0, 20)	30 (13, 55)	0.008	5 to 40
8 h	0 (0, 26)	45 (11, 76)	0.002	10 to 50
12 h	10 (0, 14)	50 (18, 70)	0.0002	15 to 60
24 h	5 (0, 20)	20 (0, 40)	ns	0 to 25

Table 7 VAS scores for pain while attempting to turn over (mm). Median (lower quartile, upper quartile) and 95% confidence intervals (CI) for the difference in the medians (mm). (No significant differences)

Time epoch	Group D	Group M	95% CI
End of surgery	0 (0, 0)	0 (0, 0)	0
2 h	0 (0, 10)	18 (0, 38)	0 to 20
3 h	23 (0, 38)	25 (10, 40)	–10 to 15
4 h	28 (0, 48)	28 (10, 50)	–10 to 20
6 h	20 (0, 46)	20 (10, 30)	–20 to 10
8 h	20 (0, 40)	20 (10, 38)	–10 to 20
12 h	15 (0, 40)	20 (10, 40)	–15 to 20
24 h	20 (10, 43)	30 (13, 40)	–10 to 20

pain during surgery and no intraoperative analgesic supplements were required although mild pulling sensations were not uncommon in either group.

Table 3 shows the use of other drugs during the first 24 h. There were no statistically significant differences betwen the groups.

During the first 4-h post-spinal period, there was a tendency towards a greater PCA morphine demand in group M (mean doses used 2.1 *vs* 4.2 mg), but this did not reach statistical significance. Thereafter there was virtually no difference in the PCA morphine requirements between the groups (table 4). Three patients in each group did not use any postoperative PCA morphine.

There were significant differences between the groups for sedation and itching (tables 5 and 6) but there were no significant differences between the VAS for pain while lying still or attempting to turn over (table 7).

Discussion

Although intrathecal morphine makes a very significant contribution towards postoperative analgesia it is said to be no better than placebo as regards the requirement for additional intraoperative analgesia.[8 12] Furthermore, it is claimed that its slow onset can limit its contribution to analgesia in the immediate postoperative period when the local anaesthetic begins to wear off.[8 13] Because of its high lipid solubility diamorphine may be expected to have a more rapid onset of action than morphine but we were unable to determine any difference between diamorphine and morphine as regards a contribution to intraoperative analgesia. No patient in either group required supplemental analgesia during surgery and this is reflected in the zero VAS scores for intraoperative pain. This lack of any need for intraoperative supplements mirrors our previous study of diamorphine compared with placebo[4] and our routine clinical practice where the need for any intraoperative supplement is extremely rare whether or not intrathecal opioids are used. With the use of the right lateral position for induction of spinal anaesthesia,[14 15] and the dose of bupivacaine used (10–14 mg), anaesthesia to touch to at least the T4 dermatome is generally achieved thus ensuring a pain free Caesarean section.[16] The above studies, using the sitting position with smaller[8] or larger[12] doses of bupivacaine, required intraoperative supplements in between 32%[8] and 13%[12] of both morphine and control patients.

Although there was no statistical difference in the PCA use of morphine between the two groups, in the immediate postoperative period (up to 4 h after spinal anaesthesia) there was a tendency for a greater PCA morphine consumption in the morphine group (mean doses 2.1 mg *vs* 4.2 mg, 95% confidence intervals 0, 3 mg). During this first period only one patient in group D used more than 7 mg morphine whereas five group M patients did so and three of the latter used the highest amount in this epoch—13, 15 and 15 mg of morphine. High PCA requirements in this early postoperative period have been noted by others using intrathecal morphine and several workers have tried combinations of lipid soluble opioids along with morphine in an attempt to enhance intraoperative and early postoperative analgesia without losing the longer term benefit of morphine in the later postoperative period. Fentanyl has been added to morphine in attempts to improve intraoperative and early postoperative analgesia with mixed results.[17–19] More recently Chung and colleagues mixed morphine and pethidine to good effect.[15] The tendency for a greater PCA requirement in the morphine groups in the early postoperative period lends support to the theoretical belief that diamorphine should have a faster onset than morphine. Based on the above results, to demonstrate this difference in early PCA requirements (2.2 mg) conclusively, then for 90% power of detecting this difference at the 0.05% significance level some 65 patients per group would be required.

As described above several published studies on the use of intrathecal morphine for analgesia after Caesarean section have been particularly noteworthy in that no patient received postoperative opioid analgesia.[5–9] Because the results of our previous study[4] indicated that some 68% of women used the PCA after intrathecal diamorphine (0.3 mg) we were very surprised to find no overall difference between the postoperative PCA opioid requirements of patients in our morphine and diamorphine groups. Indeed the PCA morphine requirements in the present study groups (median doses 5 and 5.5 mg in 24 h, table 4) were the same as those in the diamorphine group in our previous study (median PCA morphine dose 5 mg in 24 h).[4] With the exception of the first 4-h period, the median dose of PCA morphine used was identical in the two groups. We were also surprised at the very high PCA morphine demands made by some women. Women in the morphine group made the three highest demands: 43 mg, 52 mg and 55 mg PCA morphine over 24 h. This high PCA morphine demand has been noted in another recent study of intrathecal morphine for pain relief after Caesarean section where PCA morphine use after 0.1 mg intrathecal morphine ranged from 0–64 mg in 24 h.[12] This is comparable with the 0–55 mg in 24 h found in this present study. Swart, Sewell and Thomas[12] also recorded that 50% of their patients used less than 10 mg of morphine in 24 h. In the present study 70% (14 of 20) of group D and 60% (12 of 20) of group M used less than 10 mg PCA morphine over 24 h.

The literature indicates a dichotomy of opinion as to the effectiveness of intrathecal morphine. The most likely explanation for the different observations between the studies finding a significant postoperative opioid demand (the current study and Swart, Sewell and Thomas[12]) and those showing little need of postoperative opioid analgesia[5–9] lies in the methodology used to assess the need for analgesia. Whereas the present study and that of Swart, Sewell and Thomas[12] used PCA to determine a patient's need for analgesia, the studies finding a very low or no opioid use relied on nurse administered analgesia.[5–9] Furthermore, often the emphasis in these latter studies was on routine analgesia with various oral or rectal drugs[5 7] and in some cases parenteral opioids were not available or were not prescribed as routine.[5 6 8 9] PCA is the only method of determining a patient's true analgesic requirement, free of intentional or unintentional outside interference and restrictions. Because of the many confounding variables which can occur between the time when a patient first feels the need for additional analgesia and actually obtaining that analgesia from a nurse, the results of these latter studies[5–9] cannot be compared directly with PCA studies.

On the other hand, compared with the above non-PCA studies,[5–9] a major problem of the present study was the failure of patients to receive their full dose of rectal diclofenac on the prescribed regular basis. During the 24-h study period of our study eight diamorphine and nine morphine group women received only the 75-mg dose of diclofenac administered at the end of surgery. The majority of these women declined subsequent diclofenac because they were comfortable and did not wish a rectal drug.

There is a lack of information on the relative potencies of intrathecal morphine and diamorphine. Paterson and colleagues[20] observed that, intrathecally, 1.25 and 2.5 mg of diamorphine provided postoperative analgesia equivalent to 1.25 and 2.5 mg of morphine. Whether this equivalence holds for the smaller doses used today is unknown. It should also be remembered that, although one molecule of diamorphine produces one molecule of morphine, because of the different molecular weights of the two drugs 100 mg diamorphine produces 77.3 mg of morphine (thus 0.2 mg of diamorphine would produce only 0.155 mg of morphine). The situation is further confused by the quite different lipophilicity of the two drugs: the high lipid solubility of diamorphine suggests the onset of diamorphine analgesia should be more rapid than that of morphine.[21] Theoretically, one might expect that the high lipid solubility and short CSF half-life of diamorphine would lead to a limited duration of action.[21] However, clinically this is not so.[19 21 22] Although the half-life of diamorphine in the CSF after intrathecal injection is of the order of 6–8 min compared with 14–360 min for morphine[2] the duration of action of diamorphine depends on much more than the CSF concentration. Diamorphine is a pro-drug with no intrinsic opioid activity but because of its high lipid solubility it diffuses rapidly into neural tissue where esterases quickly release the active compounds 6-acetylmorphine and morphine. These latter agents, being much less lipid soluble, remain in high concentrations within the substance of the cord, thus maintaining their presence around the mu receptors, and only very slowly diffuse back into the CSF.[21] Theoretically, these pharmacokinetic properties of diamorphine suggest it should have a lower risk of centrally-mediated side effects (delayed respiratory depression, itching, drowsiness, nausea) than morphine and indeed we did observe significantly lower VAS for itching and late-onset drowsiness with diamorphine in the current study. There were also fewer individual interventions to treat itching or nausea in the diamorphine group compared with the morphine groups (5 *vs* 10). These findings reassured us that intrathecal diamorphine provides as good postoperative pain relief as morphine. Furthermore, as diamorphine has significantly reduced VAS for itching and late-onset drowsiness there seems little reason to prefer morphine to diamorphine in the UK.

In conclusion, the results of this study indicate that intrathecal diamorphine 0.2 mg or intrathecal morphine 0.2 mg have very similar effects in terms of postoperative PCA morphine requirements after Caesarean section. A larger study would be required to confirm the suggestion that diamorphine may be superior to morphine in the early postoperative period.

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Effect of clonidine on changes in plasma catecholamine concentrations and oxygen consumption caused by the cold pressor test

M. T. Taittonen, R. Aantaa and O. A. Kirvela

Summary

This study was designed to investigate whether clonidine could attenuate the increase in oxygen consumption ($\dot{V}o_2$), arterial pressure (AP) and plasma catecholamines in response to the cold pressor test (CPT), an intense stimulation of the sympathetic nervous system. Six volunteers were given clonidine (2 μg kg^{-1} and 4 μg kg^{-1}) and placebo i.m. in a random, double-blind, cross-over manner. Both clonidine doses decreased plasma catecholamine concentrations ($P<0.01$), but only the higher dose of clonidine attenuated the CPT-induced absolute increase in plasma catecholamine concentration compared with the placebo group ($P<0.01$). $\dot{V}o_2$ and AP decreased and were less after clonidine 4 μg kg^{-1} when compared with clonidine 2 μg kg^{-1} and placebo ($P<0.05$) throughout the observation period. Thus, although clonidine 4 μg kg^{-1} attenuated the catecholamine response, the increases in $\dot{V}o_2$ and AP in response to CPT were similar in all groups. (*Br. J. Anaesth.* 1998; **81**: 140–144)

Keywords: pharmacology, alpha$_2$-agonists; pharmacology, clonidine; sympathetic nervous system, cold pressor test; catecholamines; metabolism, oxygen consumption

Alpha$_2$-adrenergic agonists attenuate central and peripheral sympathetic and circulatory responses in several situations.[1] Perioperative use of clonidine, the archetypal alpha$_2$-adrenergic agonist, decreases plasma concentrations of catecholamines, attenuates neuroendocrine responses to stressful stimuli and reduces arterial pressure and arterial pressure variability.[1–3] Clonidine has also been shown to reduce perioperative oxygen consumption,[4–6] which may be of benefit in patients with decreased oxygen supply in relation to demand.[7–9]

The object of the present study was to determine whether clonidine modifies the metabolic as well as sympathetic and haemodynamic responses to a noxious stimulus. We used the cold pressor test (CPT), immersion of the hand in ice water to activate nociceptive and thermal receptors, and measured the effects of clonidine 2 and 4 μg kg^{-1} i.m. on the CPT-induced responses.[10 11] This dose range has previously been demonstrated to have beneficial effects in several clinical studies.[2 12–14]

Subjects and methods

Six healthy, non-smoking men were recruited for the study (see table 1 for details). The study was approved by the Ethics Committee of Turku University Hospital and written informed consent was obtained from each individual.

Alcoholic beverages were prohibited for 36 h before each session, and food, caffeinated drinks, or chocolate were not allowed after 22:00 on the night preceding the study session. All experiments were performed at the same time of the day (08:00–12:00) to exclude diurnal variation. The study treatment, that is, clonidine 2 μg kg^{-1} or 4 μg kg^{-1} or placebo (3 ml of NaCl 0.9 %) was given into the deltoid muscle, using double-blind cross-over technique with balanced randomization. The consecutive sessions were at least one week apart for each subject.

Upon arrival in the study area, 100 mm long ungraduated visual analogue scales with extremes at each end (VAS)[15] were used to assess baseline tiredness and dryness of mouth. After VAS assessments a 20-gauge catheter was inserted into the left radial artery for direct recording of arterial pressure and for collecting blood samples for the analysis of plasma epinephrine and norepinephrine concentrations. An 18-gauge catheter was inserted into a left forearm vein and used for fluid administration. Saline (0.9%) was infused at a rate of 100 ml h^{-1}. After cannulations the volunteers were allowed to rest in supine position for 30 min.

Continuous monitoring of heart rate (HR) using lead II of the electrocardiogram, arterial haemoglobin oxygen saturation (Sp_{O_2}) using pulse oximeter and invasive recording of systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures (Cardiocap II, Datex/Instrumentarium, Helsinki, Finland) was started. The metabolic measurements, that is, oxygen consumption ($\dot{V}o_2$), carbon dioxide production ($\dot{V}co_2$) and energy expenditure (EE) were made using an indirect calorimeter (see below). When normal unsedated subjects are first placed under the canopy, $\dot{V}o_2$, $\dot{V}co_2$ and EE increase somewhat and then decrease over 5–15 min to a fairly stable plateau.[16] Thus another 30-min period was allowed to elapse and the last minute of this period was used to determine the baseline metabolic and haemodynamic values. Immediately after these measurements arterial blood was obtained for determination of baseline plasma epinephrine and norepinephrine concentrations and the study drug was administered. The metabolic and haemodynamic

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Table 1 Subject characteristics (mean [range])

Age (yr)	Height (cm)	Weight (kg)
22.3 [20–24]	183.2 [175–192)	73.7 [65–78]

data were recorded at 10-min intervals until CPT. The program Datex-Collect(Datex/Instrumentarium, Helsinki, Finland) was used for data collection and data was stored for further processing.

Fifty minutes after study drug administration subjective dryness of mouth, pain and tiredness were recorded using the VAS-scales. Five minutes were allowed to elapse before drawing an arterial blood sample for determination of plasma epinephrine and norepinephrine concentrations. After another 5 min (60 min after study drug administration) the volunteer performed the CPT and immersed his right hand to elbow level in ice water for 90 s. During and after the CPT recording of metabolic and haemodynamic values was continued at 1-min intervals for the first 10 min and thereafter at 10-min intervals. Immediately after the CPT arterial blood was collected for the analysis of plasma epinephrine and norepinephrine concentrations.

The recording of metabolic and haemodynamic values was continued for 120 min after the CPT. At the end of the study period subjective dryness of mouth, pain during the CPT and tiredness were evaluated. Arterial blood was drawn into chilled tubes containing EDTA for determination of plasma epinephrine and norepinephrine concentrations. All samples were placed immediately on ice, and centrifuged in the cold. Plasma was removed and frozen at -80 °C for later analysis. Plasma concentrations of epinephrine and norepinephrine were measured using a high-performance liquid chromatography-electrochemical detection assay.[17]

The metabolic measurements were made by a portable metabolic cart system (Deltatrac, Datex/Instrumentarium, Helsinki, Finland) with good overall accuracy.[18] We have described this method previously in detail.[19] Briefly, the Deltatrac is an open-system, indirect calorimetry device designed to measure $\dot{V}O_2$, $\dot{V}CO_2$ and EE. For the measurement, the subject's head is placed under a plastic cone (canopy) connected to the analyser. The canopy is half-ellipsoidal and is made of 1-mm-thick transparent PVC plastic. It is provided with adapters for tubing and with a wide edge of soft plastic cloth to make the construction airtight around the head and neck of the subject. Minor leakages do not affect the results as they are directed inward because of the slight underpressure inside the canopy caused by the constant airflow (40 litre min^{-1}) drawn through the canopy to the gas analysers, and thus, all expired gases will be captured. The Deltatrac was calibrated before each measurement by the procedure suggested by the manufacturer.

Statistical analysis was performed by the SAS program (SAS institute Inc., Cary, USA) using analysis of variance (ANOVA) for repeated measurements with two within factors (dose and time). The carry-over effect was tested for each variable and no significant carry-over effects were found. The maximum response of SAP, MAP, DAP, HR, $\dot{V}O_2$, $\dot{V}CO_2$, EE, plasma epinephrine and norepinephrine concentrations to the CPT was assessed by analysing the absolute peak values during/after the CPT as well as the maximum response to the CPT (peak value during/after the CPT—the value immediately before CPT) using one-way ANOVA.

When a statistically significant dose-effect or dose × time interaction was present, the analysis was continued by applying contrasts for each pair of doses.[20]

Results

There were no significant differences in dryness of mouth, in subjective pain induced by the CPT or in tiredness between the treatments. Dryness of mouth and tiredness increased towards the end of the study period after all treatments (table 2).

Both plasma epinephrine and norepinephrine concentrations were less after clonidine 2 $\mu g\ kg^{-1}$ ($P<0.001$ and $P=0.005$, respectively in pairwise comparisons) and clonidine 4 $\mu g\ kg^{-1}$ ($P<0.001$ for both variables in pairwise comparisons) when compared with placebo (fig. 1). Plasma norepinephrine concentration was lower after 4 $\mu g\ kg^{-1}$ of clonidine than after 2 $\mu g\ kg^{-1}$ of clonidine ($P=0.002$ in pairwise comparisons). The absolute increase in plasma epinephrine and norepinephrine concentrations induced by the CPT was smaller after 4 $\mu g\ kg^{-1}$ of clonidine than placebo ($P=0.033$ and $P=0.016$, respectively in one-way ANOVA). No other statistically significant differences between the treatments were observed in plasma catecholamine concentrations.

$\dot{V}O_2$ was less after clonidine 4 $\mu g\ kg^{-1}$ than clonidine 2 $\mu g\ kg^{-1}$ or placebo ($P=0.046$ and $P=0.039$,

Table 2 VAS-scales for tiredness, dryness of mouth and pain (mean (SD)). C 2 $\mu g\ kg^{-1}$ = clonidine 2 $\mu g\ kg^{-1}$, C 4 $\mu g\ kg^{-1}$ = clonidine 4 $\mu g\ kg^{-1}$. ANOVA = *P* values for overall ANOVA, D = dose effect, T = time, T×D = dose × time interaction. I = baseline; II = 50 min after study drug; III = at the end of the study, that is, 180 min after the study drug. Pain Bl = pain before the cold pressor test (CPT), Pain CPT = pain during the CPT, measured at the end of the study.

	Study groups			
	C 2 $\mu g\ kg^{-1}$	C 4 $\mu g\ kg^{-1}$	Placebo	ANOVA
Dryness of mouth I	3.3 (8.2)	0.0 (0.0)	3.3 (8.2)	D=0.187
Dryness of mouth II	9.7 (11.4)	26.3 (31.5)	6.3 (7.2)	T=0.021
Dryness of mouth III	8.3 (7.3)	24.2 (21.9)	6.0 (6.6)	D×T=0.076
Tiredness I	8.3 (10.2)	10.8 (9.6)	8.3 (10.8)	D=0.166
Tiredness II	24.8 (18.9)	46.5 (18.3)	19.3 (18.8)	T<0.001
Tiredness III	5.8 (6.1)	19.8 (18.8)	3.8 (6.0)	D×T
Pain Bl	3.2 (1.0)	2.0 (3.0)	0.0 (0.0)	D=0.476
				T<0.001
Pain CPT	39.8 (18.0)	42.8 (19.1)	49.2 (20.5)	D×T=0.272

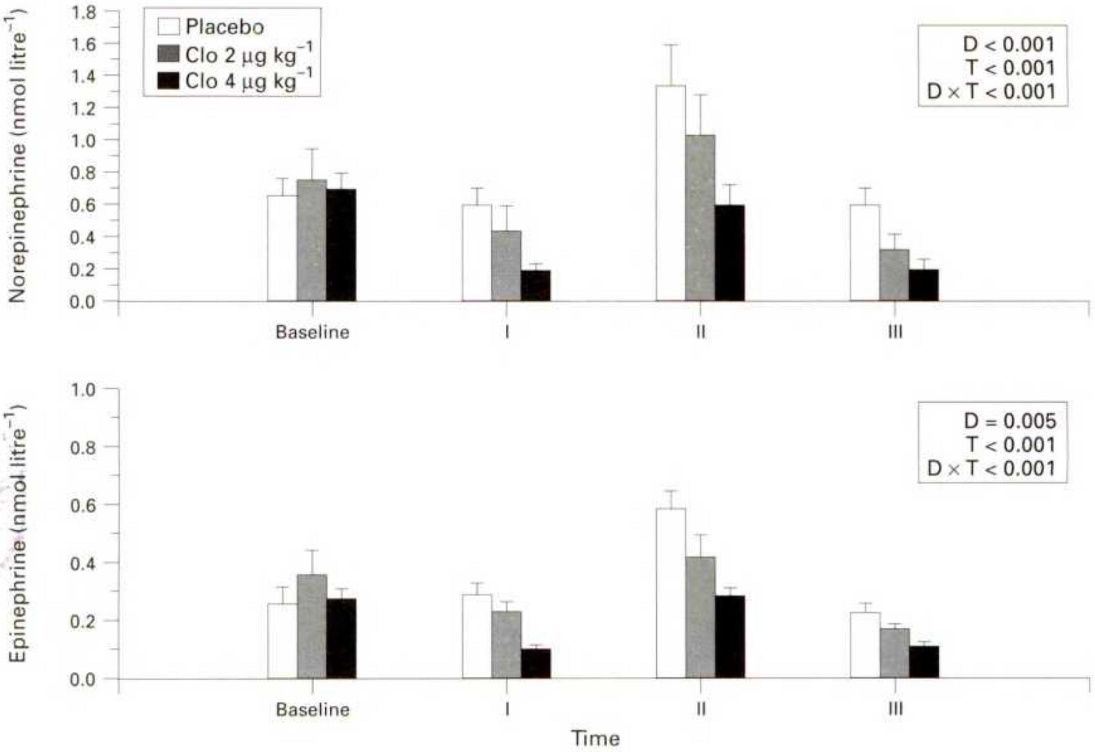

Figure 1 Plasma epinephrine and norepinephrine concentrations. Baseline= before study drug administration, I=5 min before the cold pressor test (CPT), II=immediately after the CPT, III=120 min after the CPT. Values are means (SEM). D=P value for dose-effect, T=P value for time-effect, D×T=P value for dose × time interaction in over-all ANOVA. See text for pairwise comparisons.

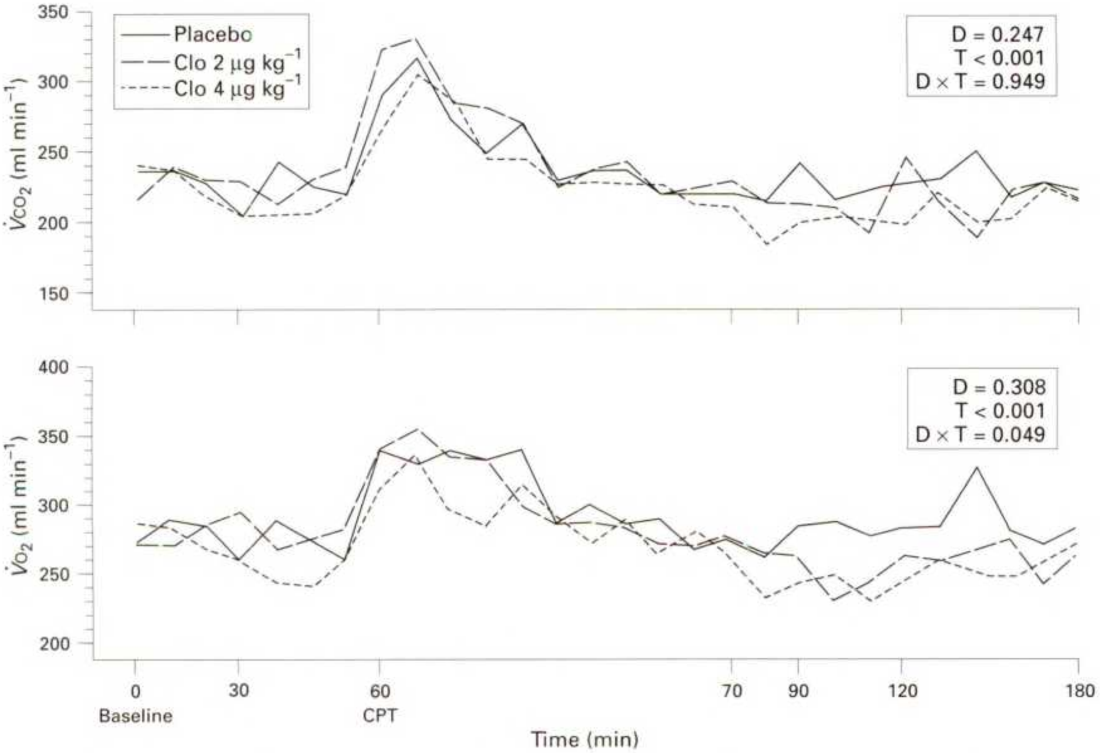

Figure 2 Oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$). CPT=the cold pressor test. Values are means. D=P value for dose-effect, T=P value for time-effect, D×T=P value for dose × time interaction in over-all ANOVA. See text for pairwise comparisons.

respectively in pairwise comparisons). The response to study treatment in $\dot{V}CO_2$ was parallel to that in $\dot{V}O_2$ (P=0.246 for drug effect and P=0.948 for drug × time interaction in overall ANOVA). The absolute increase in $\dot{V}O_2$, $\dot{V}CO_2$ and EE induced by the CPT was similar after all treatments (P=0.28, P=0.70 and P=0.45 respectively, in one-way ANOVA; fig. 2). There was a similar increase in all groups in RQ ($\dot{V}CO_2$ $\dot{V}O_2^{-1}$) during the CPT (P=0.408 for drug effect and P=0.113 for drug × time interaction in overall ANOVA). No other statistically significant differences between the treatments were observed.

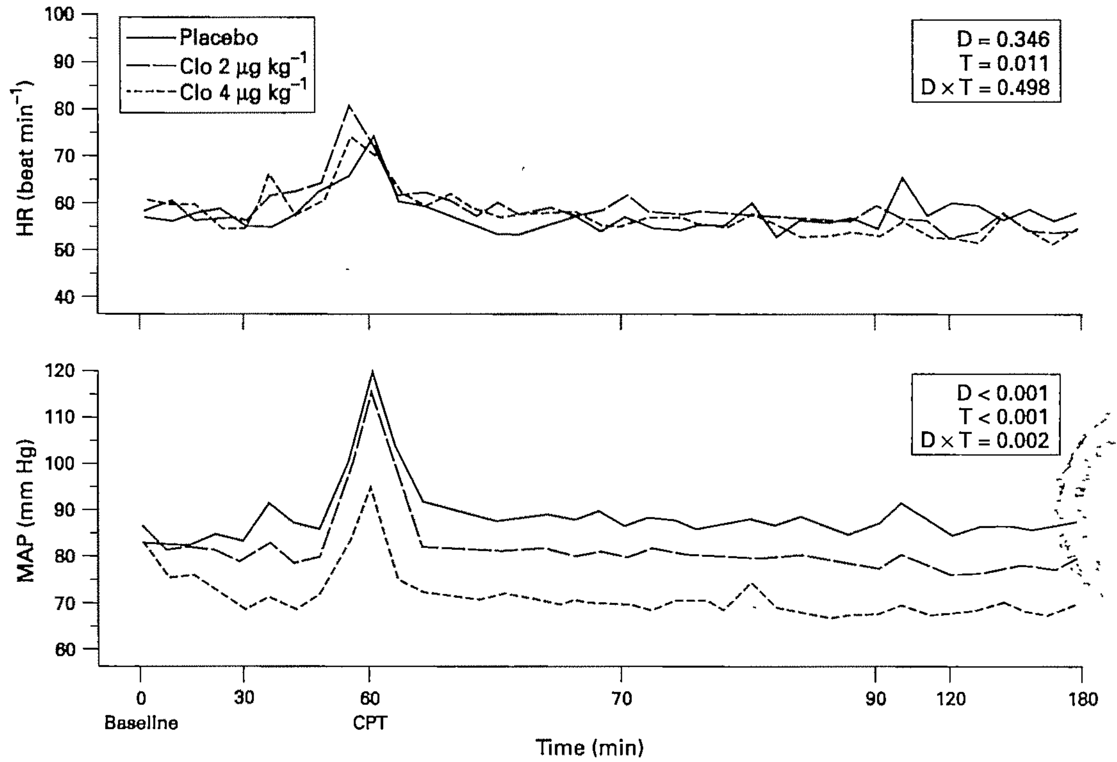

Figure 3 Heart rate (HR) and mean arterial pressure (MAP). CPT=the cold pressor test. Values are means D=*P* value for dose-effect, T=*P* value for time-effect, D×T=*P* value for dose × time interaction in over-all ANOVA. See text for pairwise comparisons.

MAP was less after clonidine 4 μg kg^{-1} than clonidine 2 μg kg^{-1} or placebo (P<0.001 and P=0.01, respectively in pairwise comparisons). The absolute increase in SAP, MAP, DAP and HR induced by the CPT was similar after all treatments (P=0.27, P=0.12, P=0.78 and P=0.82, respectively in one-way ANOVA). The peak SAP, MAP and DAP values recorded during the CPT were less after clonidine 4 μg kg^{-1} than placebo (P=0.003, P=0.016 and P=0.012, respectively in one-way ANOVA). There were no other statistically significant differences in the haemodynamic parameters between the groups (fig. 3).

No treatment had effects on Sp_{O_2}.

Discussion

Stress during and after anaesthesia and surgery is associated with increased sympathetic activity that may cause increased cardiorespiratory instability and $\dot{V}O_2$.

Alpha$_2$-agonists, including clonidine decrease central sympathetic outflow and favourably modify perioperative cardiovascular and endocrine responses to nociceptive stimuli.[1] The reduction in sympathetic activity and consequent attenuation of tachycardia and hypertension may lead to a decrease in total body $\dot{V}O_2$ which in turn may be of benefit in patients at risk of inadequate cardiac output or tissue oxygen delivery.[1-9]

In our study, i.m. clonidine (2 and 4 μg kg^{-1}) decreased plasma epinephrine and norepinephrine concentrations in a dose-dependent fashion. In addition, clonidine 4 μg kg^{-1} attenuated the catecholamine response to the CPT. This supports the results of a previous study where a fixed dose of oral clonidine 0.3 mg reduced the CPT-induced increase in plasma norepinephrine concentrations in healthy volunteers.[12] The changes in plasma catecholamine concentrations, however, reflect only peripheral catecholamine spillover and not the pharmacological mechanism of action of clonidine (that is, decrease in central nervous system sympathetic activity). First, the blood–brain barrier is almost complete for catecholamines[21] and second, plasma norepinephrine concentrations reflect the difference between the total quantity of norepinephrine released into the circulation and that removed by uptake and clearance mechanisms. Nevertheless, at times of maximal surgical stress changes in peripheral catecholamine concentrations reflect the magnitude of the central sympathetic response.[22]

Reduced sympathetic nervous system activity with consequent changes in plasma catecholamine concentrations may lead to decreased whole body $\dot{V}O_2$[3-6] as observed in our study in which $\dot{V}O_2$ decreased significantly before the CPT after the larger clonidine dose when compared with placebo. We have previously observed a similar reduction in $\dot{V}O_2$ after clonidine (4 μg kg^{-1} i.m.) in pre- and postoperative patients.[4 5] The clonidine doses used by us did not, however, attenuate $\dot{V}O_2$ response to the CPT as the maximum increase in $\dot{V}O_2$ induced by the CPT was similar after all treatments. After the CPT $\dot{V}O_2$ decreased to the pre-CPT values within 20 min. $\dot{V}O_2$ remained reduced until the end of the study period after clonidine 4 μg kg^{-1} when compared with placebo. This agrees with the pharmacokinetic parameters of clonidine, T_{max} of i.m. clonidine being approximately 54 min.[13]

We did not record or control respiratory rate or ventilation and the volunteers may have hyperventilated from the pain caused by the CPT. Hyperventilation can lead to variations in the $\dot{V}O_2$

and $\dot{V}co_2$ measurements. In this study, changes in $\dot{V}o_2$ and $\dot{V}co_2$ were parallel throughout the study except for a short period during the CPT when RQ increased slightly indicating that some hyperventilation occurred.[16] Hyperventilation may thus have attenuated gas-exchange measurements and obscured the possible differences between the treatments.

In this study clonidine 4 $\mu g\ kg^{-1}$ decreased MAP when compared with clonidine 2 $\mu g\ kg^{-1}$ and placebo. The maximum increase in AP caused by the CPT was similar in all groups, though the peak values of SAP, MAP and DAP recorded during the CPT were lower after clonidine 4 $\mu g\ kg^{-1}$ when compared with placebo. There were no significant differences in HR between the treatments. This supports recent data which have suggested that clonidine decreases AP but does not modify the pressor response to stressful stimuli such as laryngoscopy and tracheal intubation[14] or the CPT.[12] Perioperatively clonidine, in the dose range used by us, significantly attenuates the haemodynamic response to anaesthesia and surgery when used as adjunct to other anaesthetics and analgesics.[1 2] Although AP remained less after clonidine, no such attenuation of the haemodynamic responses to the CPT could be demonstrated in the present study. Alpha$_2$-agonists have significant synergistic interaction both with anaesthetic agents[1 2] and opioids[23] and thus clonidine, in the dose range used by us (2–4 $\mu g\ kg^{-1}$), may not have been sufficient to blunt the CPT-induced haemodynamic changes by itself in the present study.

As increased myocardial workload raises $\dot{V}o_2$ the cardiovascular response to the CPT may contribute to the response in $\dot{V}o_2$ observed by us after all treatments. However, as myocardial $\dot{V}o_2$ represents only 10% of the total body $\dot{V}o_2$ at rest,[24] the haemodynamic changes cannot entirely explain changes in $\dot{V}o_2$ observed in the present study after clonidine.

Pain during the CPT was tested using the VAS-scales at the end of the study to avoid interruption of the metabolic and haemodynamic measurements. There were no differences in subjective pain assessments between the treatments. Hence, in this setting no analgesic effect could be attributed to either of the clonidine doses, though the sensitivity of VAS may have been obscured by time elapsed from the CPT to assessment of pain. The lack of analgesic action may also be because of the relatively small doses of clonidine used by us.

In conclusion, clonidine decreased plasma catecholamine concentrations, $\dot{V}o_2$ and AP in a dose-dependent fashion. Clonidine (4 $\mu g\ kg^{-1}$) also attenuated the catecholamine response but did not blunt the increase in $\dot{V}o_2$, AP and HR induced by the CPT.

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I.v. clonidine prevents post-extradural shivering

S. SIA

Summary

We have studied the efficacy of i.v. clonidine to prevent shivering in 100 healthy patients who received extradural block for knee arthroscopy. Patients were randomly allocated to two groups. Just before extradural anaesthesia (0 min = baseline), group I ($n = 50$) received i.v. clonidine 1 μg kg^{-1}, group II ($n = 50$) received a saline bolus. Systolic arterial pressure (SAP), heart rate (HR), oxygen saturation (Sp_{O_2}), cutaneous temperature and level of sedation, were all recorded at baseline and after 10, 20, 30, 45, 60 min. Shivering was evaluated by a blinded investigator for a period of 90 min and was graded as moderate or severe. Three patients in group I shivered compared with 19 in group II ($P < 0.001$). Patients with severe shivering were seen only in group II. There were no significant differences between the groups during the study period in SAP, HR, Sp_{O_2}, cutaneous temperature or level of sedation. We conclude that preventive use of i.v. clonidine 1 μg kg^{-1} provides a significant reduction in the incidence of post-extradural shivering without clinically relevant adverse side effects. (*Br. J. Anaesth.* 1998; **81**: 145–146)

Keywords: anaesthetic techniques, extradural; complications, shivering; pharmacology, clonidine

Shivering is a common and distressing side effect of extradural anaesthesia. Clonidine has been shown to suppress established shivering after general[1] and extradural anaesthesia.[2] Recent studies have suggested that prophylactic use of clonidine prevents the development of shivering after general anaesthesia.[3–5] To date, no evidence has been published to show that preventive use of clonidine reduces the incidence of shivering after extradural anaesthesia. This randomized, double-blind study was performed to evaluate the effects of i.v. clonidine given just before extradural anaesthesia on the incidence and severity of shivering in patients undergoing orthopaedic surgery.

Patients and methods

After institutional approval, informed consent was obtained from 100 patients, ASA physical status I–II, scheduled for knee arthroscopy under extradural anaesthesia. No premedication was given. Patients were randomly assigned to one of two groups. In group I ($n = 50$) clonidine 1 μg kg^{-1} in 2 ml saline was given i.v. just before extradural anaesthesia (0 min = baseline). Group II patients ($n = 50$) were given the same volume of saline at the same time. Extradural anaesthesia was performed at L3–L4 or L4–L5 interspace with 2% mepivacaine (15–20 ml). All patients received an i.v. infusion of 12 ml kg^{-1} h^{-1} of a crystalloid solution. Patients wore shorts and a light cotton shirt and were draped with a single cotton blanket. During the intra-operative period all patients were completely covered in surgical drapes except for the head and neck area. A space blanket was used in all patients from baseline until the end of the study period (90 min). No means of active warming were used. All operations were performed in the same operating room which was maintained at a constant temperature of 22 ± 1°C. The operating room was not equipped to provide laminar flow. The rate of air turnover was 18/h. Systolic arterial pressure (SAP), heart rate (HR), arterial oxygen saturation (Sp_{O_2}), peripheral temperature, sedation score (0 = alert, 1 = awake but drowsy, 2 = asleep but arousable, 3 = unrousable) and thermal perception score were all recorded at baseline and after 10, 20, 30, 45 and 60 min. Thermal perception was evaluated with a 100-mm visual analogue scale (VAS), ranging from "worst imaginable cold" to "insufferably hot". A decrease in SAP of more than 20% of the baseline values was treated with ephedrine 5 mg i.v. and HR under 50 bpm with atropine i.v. 0.5 mg. A blinded investigator recorded the incidence of visible shivering for a period of 90 min from baseline. Shivering was graded using a 3-point scale (0 = absent; 1 = moderate; 2 = severe). Statistical analysis was performed using the one-way analysis of variance, two-way analysis of variance for repeated measures, chi-square test or Mann–Whitney U test as appropriate. Data are presented as mean (SD); $P < 0.05$ was considered significant. All analyses were carried out using SIMSTAT statistical analysis package version 3.5 for DOS.

Results

Patient, anaesthetic and surgical variables and baseline values, were similar in the two groups (table 1). The overall incidence of shivering was lower in group I than in group II: three of the clonidine-treated patients had shivering compared with 19 in the placebo group ($P < 0.001$). The intensity of shivering was lower in group I than in group II ($P < 0.01$). Moderate shivering was observed in three patients in group I and six patients in group II, severe shivering

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Table 1 Morphometric data, anaesthetic variables and postanaesthetic shivering (mean (SD)). $^{*}P < 0.001$

	Group I	Group II
Age (yr) [range]	29 [18–42]	32 [18–44]
Gender (m / f)	13/19	35/15
Weight (kg)	64 (13)	66 (11)
Height (cm)	171 (8)	169 (10)
Duration of surgery (min)	28 (9)	30 (10)
Max level of anaesthesia at 30 min	T9 (2)	T9 (1)
Baseline peripheral temperature (°C)	33.1 (0.8)	32.9 (0.6)
Patients shivering (n)	3	19*
Patients with moderate shivering (n)	3	6
Patients with severe shivering (n)	0	13*
Time from baseline to onset of shivering (min)	38 (5)	40 (11)
Duration of shivering (min)	22 (6)	27 (9)

occurred in 13 patients in group II and in none in group I ($P < 0.001$). The time of onset and the duration of shivering did not differ significantly between the groups (table 1). Sp_{O_2} exceeded 96% in all patients at all times. The degree of sedation was negligible in both groups, before and after the drug treatment. Thermal perception score increased significantly with respect to baseline at 45 and 60 min in group I and at 30, 45, 60 min in group II, this was not significant between the groups (see table 2). Peripheral temperature did not differ significantly from baseline during the study period in either group. SAP and HR decreased significantly with respect to baseline at 20 and 30 min in both groups. However, there was no significant difference between the groups at any time (see table 2). The number of patients receiving vasoactive agents was similar in both groups (7 *vs* 8). Four of the eight patients in group I received atropine 0.5 mg, two received ephedrine 5 mg and one received both atropine and ephedrine. Five of the eight patients in group II received atropine 0.5 mg and three received ephedrine 5 mg.

Discussion

Our results demonstrate that the incidence of shivering was significantly lower in patients receiving clonidine than in the control group. There is considerable experimental evidence that shivering during extradural anaesthesia is thermoregulatory, triggered by central compartment (core) hypothermia.[6] Redistribution of heat from the core to the periphery seems to be the most important aetiology of hypothermia caused by extradural anaesthesia.[6 7] The mechanism by which clonidine prevents or stops shivering is not well understood. Clonidine may act on hypothalamic alpha-2 adrenergic receptors, impairing central thermoregulatory control, in particular lowering the shivering threshold.[8] In volunteers given a bolus of clonidine just before their core temperature was cooled by central venous infusion of cold saline, thermoregulatory shivering occurred at a lower core temperature than in those given placebo.[8] Clonidine-induced reduction of the shivering threshold was dose-dependent and i.v. bolus seems to be the most effective route of administration.[8] Therefore, to give an i.v. bolus of clonidine just before redistribution of central heat induced by extradural anaesthesia may be a logical approach to preventing shivering. Prevention of shivering by clonidine use may be limited by its principal side effects such as hypotension, bradycardia and sedation. In our study, a bolus injection of clonidine was not associated with significant changes in systemic haemodynamic variables, probably because of the low dose used. We did not need to give an increased dose of vasoactive drugs in the clonidine-treated patients. Sedation scores and Sp_{O_2} were not altered by clonidine use. We conclude that preventive use of i.v. clonidine 1 μg kg^{-1} provides a significant reduction in the incidence of post-extradural shivering without clinically relevant adverse side effects.

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Table 2 Values of systolic arterial pressure (SAP), heart rate (HR), thermal perception score and sedation score during the study period. Data are presented as mean(SD). * $P < 0.05$ *vs* baseline, ** $P < 0.01$ *vs* baseline

Time (min)	SAP (mm Hg)		HR (beat min^{-1})		Thermal perception score (mm)		Sedation score	
	group I	group II	group I	group II	group I	group II	group I	group II
baseline	121 (15)	120 (15)	82 (10)	85 (10)	3.9 (0.7)	4.0 (0.6)	0.04 (0.2)	0.02 (0.14)
10	119 (12)	116 (11)	82 (12)	82 (12)	3.8 (1.0)	4.0 (0.7)	0.06 (0.31)	0.06 (0.24)
20	114 (15)*	113 (12)*	77 (11)*	80 (11)*	4.0 (0.9)	4.3 (1.0)	0.1 (0.36)	0.12 (0.39)
30	113 (13)**	112 (14)**	76 (11)**	79 (10)**	4.3 (1.3)	4.4 (1.0)*	0.14 (0.45)	0.16 (0.51)
45	118 (15)	118 (14)	79 (13)	83 (12)	4.4 (1.3)*	4.6 (1.4)**	0.14 (0.5)	0.12 (0.39)
60	119 (12)	121 (13)	80 (13)	84 (11)	4.6 (1.7)**	4.6 (1.5)*	0.14 (0.45)	0.12 (0.44)

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Pharmacological vasodilatation improves efficiency of rewarming from hypothermic cardiopulmonary bypass

C. D. Deakin, G. W. Petley and D. Smith

Summary

An afterdrop in core temperature after hypothermic cardiopulmonary bypass (CPB) is related to inadequate peripheral rewarming. We proposed that pharmacological vasodilatation during rewarming on bypass would improve peripheral rewarming and reduce the degree of afterdrop. Fifty-nine of 120 patients were randomized to receive a sodium nitroprusside (SNP) infusion during the rewarming stage of hypothermic CPB. Mean systemic vascular resistance (SVR) during the rewarming phase of CPB was 1129 dyne s^{-1} cm^{-5} in the control group and 768 dyne s^{-1} m^{-5} in the SNP group ($P \leq 0.001$). Patients receiving SNP rewarmed to 37.0 °C faster (299 min *vs* 376 min; P=0.003) and were extubated earlier (490 min *vs* 621 min; P=0.001). Patients receiving SNP had a warmer mean peripheral temperature (MPT) (32.9 °C *vs* 32.4 °C; P=0.05) on termination of CPB. Postoperative core temperature fell less in the SNP group (35.6 °C *vs* 35.2 °C; P=0.01) as did MPT (31.8 °C *vs* 31.2 °C; P=0.004). SNP-induced vasodilatation during rewarming from hypothermic CPB improves peripheral rewarming, reduces the degree of postoperative core and peripheral hypothermia and reduces time to extubation. (*Br. J. Anaesth.* 1998; **81**: 147–151)

Keywords: surgery, cardiopulmonary bypass; hypothermia; sodium nitroprusside

During hypothermic cardiopulmonary bypass (CPB), core temperature is usually reduced to below 30 °C to reduce tissue oxygen consumption and afford some degree of cerebral and myocardial protection. Despite apparently adequate rewarming as judged by a normal core temperature on termination of CPB, moderate postoperative hypothermia is common.[1,2] Morbidity from postoperative hypothermia includes increased time to extubation, increased myocardial work and oxygen consumption, impaired coagulation,[3,4] increased risk of wound infection and prolonged hospital stay.[5] Postoperative hypothermia cannot be explained by heat loss to the environment alone and is thought to result from a failure of heat transfer to vasoconstricted peripheral tissues during rewarming on CPB, with a subsequent shift of heat from a warm core to a cold periphery.[4,6] Increasing blood flow to vascular beds by increasing pump flow during rewarming on bypass reduces the degree of postoperative hypothermia,[7] but the resultant pressure in the arterial cannula of the extracorporeal circuit may cause mechanical damage to blood. Pharmacologically-induced vasodilatation has been proposed as a method to limit postoperative hypothermia[6] by improving rewarming of constricted vascular beds. In this previous study, pharmacological vasodilatation was combined with increased pump flow, and therefore increased heat delivery to the patient, so that the contribution of each factor to the subsequent reduction in postoperative hypothermia was unclear. This study was designed to determine whether pharmacological vasodilatation alone during the rewarming phase of hypothermic CPB would improve the efficiency of rewarming and reduce postoperative hypothermia.

Patients and methods

After obtaining local Ethics Committee approval, 120 sequential patients undergoing elective first-time coronary artery bypass grafting or valve replacement, or both, were entered into the study after written informed consent. Patients with peripheral vascular disease, diabetes mellitus or those subsequently returning to theatre for operation were excluded. Using a binary random number generator, patients were randomly assigned to a control group or to receive sodium nitroprusside (SNP). SNP was administered via a syringe driver (Graseby 3400) from the start of rewarming on CPB to the termination of CPB at a rate adjusted manually to give a mean arterial pressure (MAP) of 40 mm Hg. MAP during rewarming in the control group was not adjusted other than to maintain MAP below 80 mm Hg using 1-mg increments of phentolamine as is our usual practice. Patients receiving SNP did not receive inotropic or vasoconstrictor agents concurrently. Peri-operative management was otherwise identical in both groups.

Patients received lorazepam 2 mg orally 2 h before operation followed by morphine 5–10 mg i.m. and scopolamine 0.2–0.4 mg i.m. 1 h before surgery. Radial artery and peripheral venous cannulas were inserted under local anaesthesia. Anaesthesia was induced using midazolam 0.02–0.05 mg kg^{-1} i.v., fentanyl 10–15 μg kg^{-1} i.v. and pancuronium 0.1 mg kg^{-1} i.v. The trachea was intubated and the lungs mechanically ventilated using oxygen in nitrous oxide, adjusted to maintain normocapnia. A heat and moisture exchanger was placed in the breathing circuit. A

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central venous catheter was then inserted. Anaesthesia was maintained using propofol 80–150 mg h^{-1} and isoflurane to 1.2% as necessary. Midazolam 4 mg and pancuronium 4 mg were added to the pump prime fluid.

Core temperature was measured using a calibrated tympanic membrane thermocouple temperature probe (Mallinckrodt, Northampton, UK) placed before induction of anaesthesia after visually confirming with an otoscope that the external auditory meatus was free from wax. Peripheral temperature was recorded using four calibrated thermistors (Yellow Springs 400) placed on the chest wall, upper arm, thigh and calf before induction of anaesthesia. Mean skin temperature (MST) was calculated using a weighted equation as described by Ramanathan[8]:

$$MST=0.3\ (\text{chest wall}+\text{upper arm})+0.2\ (\text{leg}+\text{thigh})$$

All temperatures were recorded to a temperature logger[9] at 1-min intervals from induction of anaesthesia until postoperative core temperature had returned to 37.0 °C.

The CPB unit incorporated a Dideco D703 (Sorin, Italy) hollow fibre membrane oxygenator with integral heat exchanger primed with lactated Ringer's solution. During hypothermic CPB, core temperatures were reduced to 28–30 °C. Pump flow during cooling and rewarming was adjusted according to a standardized local procedure. Flow was indexed at 2.4 litre min^{-1} m^{-2} above 30 °C, 1.8 litre min^{-1} m^{-2} between 28–30 °C, and 1.2 litre min^{-1} m^{-2} below 28 °C, except during cooling when it was reduced to approximately 1.2 litre min^{-1} m^{-2}. Rewarming aimed to restore the patients core temperature to 37 °C before termination of CPB.

Heat extracted and returned to patients whilst on CPB was recorded using a previously described energy balance machine.[10] The apparatus comprised an IBM compatible personal computer running dedicated software which interactively collects data from a specifically designed energy flux measurement system. The calculation of energy balance is based upon the Fick principle using pump flow and arterial and venous temperature in the perfusion circuit.

Net thermal energy balance (TEB) is calculated from the equation:

$$E=sp\int_0^t (Ta-Tv)\,Q(t)\,\delta t$$

where: E=net thermal energy balance during CPB (kJ), Q=pump flow at time t (litre min^{-1}), s=specific heat capacity of blood (3.84 kJ kg^{-1} °C), p=density of perfusate (approximately 1.0 kg $litre^{-1}$), a=arterial infusion temperature (°C), Tv=venous infusion temperature (°C), t=time.

The temperatures of arterial and venous blood were recorded at the inflow and outflow to the heat exchanger/oxygenator unit using previously calibrated thermistor probes (Electromedics Inc, Englewood CO 80112 USA, model No 4700 M344700) specifically adapted to fit the gold insulated temperature probe ports on the inflow to the heat exchanger (Tv) and the outflow from the oxygenator (Ta). Rotation of the pump was detected by an infrared reflective sensor placed over the pump head cover. As a marked limb passed beneath the detector, the sensor registered one rotation equivalent to 46-ml volume. The energy flux measured each minute was summated to give an instantaneous TEB. TEB is thus zero at commencement of bypass, becomes negative as the patient is cooled, and returns to a positive value as the patient is rewarmed before termination of bypass.

Operating theatre and intensive care environments were maintained at a stable state as allowed by the air conditioning. Operating theatre temperature was maintained between 20–24 °C and relative humidity between 38–50%. Temperature in the intensive care unit was maintained between 22–25 °C. No heating/cooling mattress was used during the operation. After bypass, all i.v. crystalloid, colloid and blood products were administered through a blood warmer heated to 37.8 °C until core temperature reached 37 °C. Patients were covered by a standard hospital woollen blanket and cotton sheet. No active postoperative warming was used.

Adequacy of rewarming was assessed by recording the coldest postoperative core temperature following termination of CPB (fig. 1A) and the time for the postoperative core temperature to return to 37 °C following afterdrop (fig. 1B). Time rewarming on bypass was the time from the start of rewarming to the termination of CPB (fig. 1C). Time to extubation was the time from the end of bypass to extubation of the patient. The doctor deciding when to extubate the patient was blinded to the group to which the patient was allocated. Statistical analysis was performed with Microsoft Excel 5.0 using unpaired two-way *t* tests. Results are given as mean values with confidence intervals (CI) for the mean difference between the control and SNP group. Significance was taken as $P \leq 0.05$.

Results

One hundred and twenty patients were studied, of whom 59 were randomly assigned to receive SNP. There was no significant difference between control

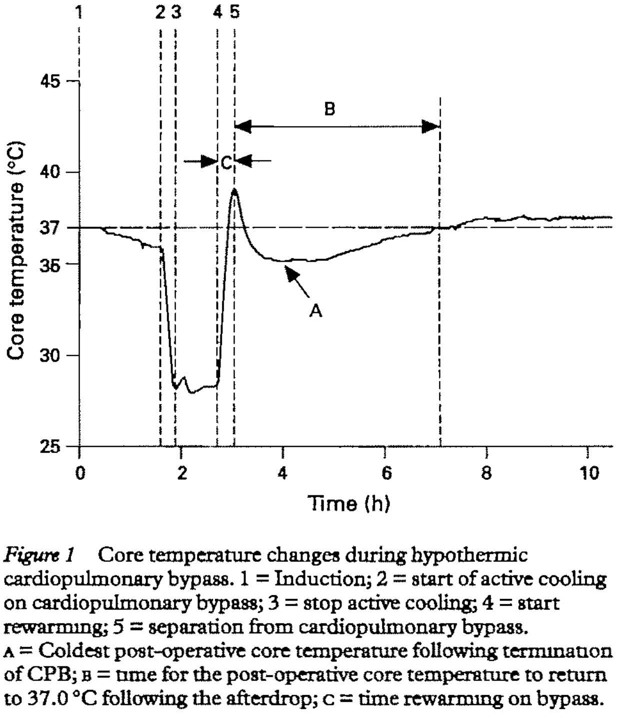

Figure 1 Core temperature changes during hypothermic cardiopulmonary bypass. 1 = Induction; 2 = start of active cooling on cardiopulmonary bypass; 3 = stop active cooling; 4 = start rewarming; 5 = separation from cardiopulmonary bypass. A = Coldest post-operative core temperature following termination of CPB; B = time for the post-operative core temperature to return to 37.0 °C following the afterdrop; C = time rewarming on bypass.

and SNP groups in patient characteristics or environmental conditions. Patient characteristics are given in table 1. Ventilation was controlled manually for two patients in the control group for a prolonged period because of cardiovascular instability in one patient and postoperative bleeding in the other. Time to extubation of these patients was therefore excluded from the data. The power of the study was calculated from the time to rewarm to 37 °C in both groups. Standardized difference was 0.564 giving a power of 0.87 using the nomogram described by Altman.[11] Mean arterial pressure during the rewarming phase of CPB was 53.5 mm Hg in the control group and 40.1 mm Hg in the SNP group (95%CI 10.8 to 15.9 mm Hg; $P \leq 0.001$). This equates to a mean systemic vascular resistance (SVR) of 1129 dyne s^{-1} cm^{-5} and 768 dyne s^{-1} cm^{-5} respectively. There was no significant difference in the amount of perioperative i.v. fluid administered to the two groups.

Time to rewarm to 37 °C was 376 min in the control group compared with 299 min in the SNP group (95%CI 28 to 129 min; $P=0.003$). Time to extubation was 621 min in the control group compared with 490 min in the SNP group (95%CI 70 to 232 min; $P=0.001$).

Patients receiving SNP had a warmer MST on termination of bypass (32.9 °C) compared with the control group (32.4 °C) (95%CI 0.06 to 0.94 °C; $P=0.05$). There was no difference in core temperature on termination of bypass between the control group (38 °C) and SNP group (38.1 °C) (95%CI -0.41 to 0.18°C; $P=0.52$).

Postoperative core temperature decreased further in the control group (35.2 °C) than the SNP group (35.6 °C) (95%CI 0.1 to 0.6 °C; $P=0.01$). Minimum postoperative peripheral temperature was warmer in the group receiving SNP (31.8 °C) compared with control (31.2 °C) (95%CI 0.14 to 0.90 °C; $P=0.004$). Once postoperative core temperature had returned to 37.0°C, there was no difference in the core–peripheral temperature difference between the control (3.65 °C) and SNP groups (3.59 °C) (95%CI -0.3 to 0.5; $P=0.72$).

There was no difference in time spent rewarming on bypass between control group (30.6 min) or SNP group (31.8 min) (95%CI -2.8 to 5.2 min; $P=0.55$). Bypass pump flows during rewarming were 8.4% higher in the SNP group (control 3.92 compared with SNP 4.25 litre min^{-1}; 95%CI 0.17 to 0.48 litre min^{-1}; $P<0.001$). Although there was no difference in mean thermal energy balance between control (805 kJ) and SNP groups (764 kJ) (95%CI -59.9 kJ to 141.7 kJ; $P=0.42$), a power of 0.05 was insufficient to conclude that this was a true negative result.

Discussion

Our results showed that pharmacological vasodilatation with SNP during the rewarming phase of CPB rewarmed the patient more efficiently as shown by warmer peripheral temperatures on termination of bypass, suggesting that heat transfer to peripheral vascular beds had been increased through increased blood flow. The subsequent postoperative hypothermia was less in patients receiving SNP, shown by greater postoperative minimum core and peripheral temperatures and shorter time to rewarm to 37°C. Clinically, improved rewarming resulted in earlier extubation.

Postoperative hypothermia is commonly seen in patients after hypothermic CPB and is greater than that observed in patients undergoing thoracic operations not requiring the use of CPB.[12] Hypothermia during CPB causes intense vasoconstriction and greatly reduces blood flow through peripheral vascular beds such as muscle and fat. During the rewarming phase of CPB, the periphery is slow to warm because of the reduced blood supply to these vascular beds and the periphery remains relatively hypothermic when CPB is discontinued, despite attainment of a normal core temperature.[13] Once bypass is discontinued, the core temperature decreases as heat is transferred to the cold periphery. Evidence for this theory is growing.[4 6] Pharmacological vasodilatation may force the periphery to vasodilate during rewarming, increase blood flow and heat transfer to the cold peripheral tissues, thereby reducing the subsequent decrease in core temperature.

The use of vasodilatation during rewarming from hypothermia on CPB was first reported by Noback and Tinker.[6] Twenty control patients were compared with eight patients receiving SNP during rewarming on bypass. SNP was administered at a rate to maintain MAP ≥70 mm Hg as CPB pump flows were increased. Increased CPB pump flow alone during rewarming increases perfusion of muscle beds and reduces the degree of postoperative hypothermia.[7] Thus, although the study of Noback and Tinker reduced the degree of postoperative hypothermia,[6] the relative contribution of increased heat delivery

Table 1 Patient characteristics and environmental conditions

	Control group	SNP group	95%CI of mean difference between groups	*P*
Theatre temp. (°C)	22.2	22.3	–0.20 to 0.37	0.64
ITU temp. (°C)	23.7	23.7	–0.32 to 0.41	0.98
Age (yr)	65.7	64.0	–2.40 to 5.81	0.41
Weight (kg)	71.9	77.0	–0.2 to 10.4	0.06
Height (cm)	169.0	170.3	–2.22 to 4.91	0 46
Body mass index (kg m^{-2})	25.1	26.4	–0.01 to 0.14	0.09
Body surface area (m^2)	1.82	1.88	–0.22 to 2.81	0.08
Mean SNP dose (μg kg^{-1} min^{-1})		1.40	±1.15 (SD)	
Rate of post-op. propofol infusion (ml h^{-1})	13.2	13.2	–0.97 to 1.14	0.87
Cardioplegia volume (ml)	1227	1179	–58 to 154	0.37

and pharmacological vasodilatation is difficult to distinguish.

Aps, Hutter and Williams[14] reviewed the postoperative progress of 143 cardiac surgery patients in whom specific attempts to ensure adequate rewarming on bypass had been made. Patients received infusions of either SNP or glyceryl trinitrate (GTN) at a maximum rate that still allowed for adequate arterial perfusion pressures during rewarming on bypass (details not given). Rewarming was further optimized by the use of patient insulation, use of a warming mattress and heating of inspiratory gases to 40 °C. Although this technique minimized the degree of postoperative hypothermia, the relative contributions of each technique cannot be distinguished.

Both GTN and SNP have been used as peripheral vasodilators in these earlier studies. Recent work suggests that both GTN and SNP have similar arteriovenous vasodilatory profiles.[15] SNP however was chosen in preference to GTN for this study because its greater potency and shorter half-life make it more suitable for acute haemodynamic manipulation. SNP dilates large arteries,[16] small arteries and arterioles,[15] increases limb blood flow through vasodilatation of skeletal muscle vasculature[17] and increases skin perfusion.[18] SNP is not known to possess any thermogenic properties.

By using the same rewarming plan for control and SNP groups, we hoped to achieve the same bypass flow rates during rewarming in both groups. Surprisingly, flow was 8.4% higher (P<0.001) in the SNP group. Although it may be expected that increased flow would be associated with increased heat delivery (TEB) during rewarming to the SNP group, the power of 0.05 for these data is insufficient to distinguish any difference between the two groups. Although the relative contribution of increased CPB flow and vasodilatation to heat transfer cannot be distinguished directly, the small difference in CPB flow between our two groups and the differential changes in core–peripheral temperature in the SNP group leads us to believe that SNP was at least partially responsible for the observed differences.

In addition, the core temperature at the end of bypass was the same in both groups. We therefore believe that the observed differences between the control and SNP groups are attributable, at least in part, to the effects of pharmacological vasodilatation. The larger differences in peripheral temperature between the control and SNP groups observed by Noback and Tinker[6] may be caused by higher flows enabling a higher rate of SNP infusion and a greater degree of peripheral vasodilatation.

We avoided the use of warming blankets during rewarming from bypass and forced warm air convection blankets postoperatively because vasodilatation combined with active surface warming increases heat transfer to the patient[19] and may mask the effects of thermal energy redistribution in the body caused by the SNP infusion. Noback and Tinker used heating mattresses during the rewarming phase of CPB in 16 of the 20 patients in the control group and 6 of the 8 patients in the SNP group.[6] They failed to show any difference between the two groups but this may be because of the small numbers in the study.

Operating room and intensive care unit temperature varied by up to 4.0 °C. Other studies investigating postoperative rewarming have been unable to control ambient temperature more closely than our study[6] or do not report environmental conditions.[20–22] Environmental temperature did not show any significant correlation with time to rewarm to 37 °C or coldest postoperative temperature.

By increasing peripheral blood flow, SNP administered during rewarming on bypass appears to improve the efficiency of peripheral rewarming and reduce the degree of postoperative hypothermia.

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Perioperative pharmacokinetics of transdermal fentanyl in elderly and young adult patients†

J. P. THOMPSON, S. BOWER, A. M. LIDDLE AND D. J. ROWBOTHAM

Summary

The perioperative pharmacokinetics of transdermally-delivered fentanyl were compared in 10 young adult (mean [range] age 32.7, [25–38] yr) and eight elderly (mean [range] age 73.7 [64–82] yr) patients following abdominal surgery. Transdermal fentanyl patches designed to release 50 μg h^{-1} were applied 2 h preoperatively and left in place for 72 h. Plasma fentanyl concentrations were measured by radioimmunoassay during patch application and for 30 h after patch removal. The mean half-time (time for plasma concentrations to double after patch application) was 4.2 h in the younger group and 11.1 h in the elderly group ($P < 0.005$). Mean maximum plasma concentrations were 1.9 ng ml^{-1} and 1.5 ng ml^{-1} in the younger and elderly groups respectively (ns). There were no differences in the time at which maximum plasma concentrations occurred (t_{max}), elimination half-life after patch removal, or $AUC_{(0-\infty)}$. (*Br. J. Anaesth.* 1998; **81**: 152–154)

Keywords: pharmacokinetics, transdermal; pharmacology, fentanyl; analgesia, perioperative

Fentanyl may be delivered via a transdermal patch and is now available in the United Kingdom for the relief of chronic, intractable cancer pain. It has several advantages in this setting over other analgesic strategies.[1] Although not recommended for the treatment of postoperative pain, such patients present for surgery and it may be appropriate to continue the use of the fentanyl patch in the perioperative period. In healthy volunteers, systemic absorption of fentanyl reaches a plateau approximately 14 h after transdermal application, and continues for several hours after patch removal.[2] A previous study of fentanyl pharmacokinetics following i.v. administration suggested that the terminal half-life might be altered in the elderly.[3] Perioperative transdermal fentanyl pharmacokinetics have been described,[4] but there are few data comparing younger and elderly patients.

Methods

After obtaining written informed consent and local ethical research committee approval, 10 younger adult (aged 18–40 yr) and nine elderly (aged >60 yr) patients scheduled to undergo lower abdominal surgery were recruited to the study. Exclusion criteria were ASA >III patients; significant CNS, respiratory, cardiac, renal or endocrine disease; or if they were considered unable to operate a patient-controlled analgesia (PCA) system. Premedication comprized oral temazepam 20 mg 2 h preoperatively. At this time, a fentanyl transdermal patch designed to release 50 μg h^{-1} was applied to the upper anterior chest wall. Anaesthesia was induced with a sleep dose of thiopental, and maintained with 1–2% enflurane and nitrous oxide in oxygen 33%. Tracheal intubation was facilitated with atracurium 0.5 mg kg^{-1} and the lungs ventilated to normocapnia. Younger patients received morphine 0.2 mg kg^{-1} and older patients 0.1 mg kg^{-1} i.v. Residual neuromuscular block was reversed with neostigmine 2.5 mg and atropine 1.2 mg. Immediately on waking, an i.v. morphine PCA device was set up (2 mg bolus, lockout time 5 min). After 90 min, the PCA morphine bolus was reduced to 1 mg. The total amount of morphine administered by the PCA system was recorded from the data logger. The transdermal fentanyl patch remained in place for 72 h.

Patients' conscious level, respiratory rate, and pulse oximetry (Sp_{O_2}) were monitored continuously for 24 h after surgery. If respiratory rate fell below 8 breaths per minute, arterial blood-gas levels were measured; if Sp_{O_2} fell below 90% or Pa_{CO_2} was above 7.3 kPa, the fentanyl patch was removed and naloxone given as required. Blood samples (5 ml) were withdrawn from an indwelling i.v. cannula at 0, 2, 8, 12, 20, 24, 30, 48, 54 and 72 h after patch application. Further samples were taken at 0.5, 1, 2, 4, 6, 10, 20, and 30 h after patch removal. Plasma was separated by centrifugation and stored at −20°C. Fentanyl concentrations were measured by radioimmunoassay. The sensitivity and coefficient of variation of this assay have been reported previously as 2 pg ml^{-1} and 6.4% respectively.[5] Data were compared using unpaired *t* tests.

PHARMACOKINETIC VALUES

In order to compare the rise in plasma fentanyl concentration after patch application, the individual concentration-time curves up to 48 h (by which time

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the plateau concentration had been reached) were analysed by computer-generated non-linear regression using a one phase exponential association curve (Graphpad Prism version 2.0), so that Y = Ymax (1–exp [-K×x]). The equation assumes that the data start at Y=0 and ascend to Ymax with a rate constant K. A convergent fit was found for all data. Half-time, representing the time for plasma concentrations to double, was calculated as 0.693/K and compared between the groups (table 1). The rate constant for the decline in concentrations after patch removal, β, was obtained by linear regression of the terminal points after patch removal. Plasma $t_{1/2}$ was calculated as $0.693/\beta$. The area under the curve from application to infinity $AUC_{(0-\infty)}$ was calculated by the trapezoidal rule. The mean maximum observed concentration (c_{max}) and the time at which this occurred (t_{max}) were also determined.

Results

As one elderly patient received i.v. fentanyl at induction, the data from this patient were not analysed. Patches were removed before the end of the study in three elderly patients (two cases of respiratory depression after 16h and 26 h, one postoperative haemorrhage after 24 h) and two young patients (one nausea after 32 h, one dislike of blood sampling after 34 h). All patients in the younger group (mean [range] age 32.7 [25–38] yr) were women undergoing hysterectomy and/or salpingo-oophorectomy. Data for each patient were included up to the last sampling point before patch removal. The older group (mean [range] age 73.7 [64–82] yr) comprised six women and three men undergoing general surgical procedures including colostomy, colectomy and abdomino-perineal resection. There were no significant differences in supplemental morphine consumption between the groups.

Mean plasma fentanyl concentrations are shown in figure 1 and pharmacokinetic parameters in table 1. Plasma fentanyl concentrations increased to reach a plateau approximately 16–24 h after patch application and declined slowly following patch removal (at 72 h). The increase in plasma fentanyl concentrations occurred more slowly in the elderly patients, as demonstrated by the mean half-time of 11.1 h, compared with 4.2 h in the younger group. Mean maximum plasma concentrations (c_{max}), the time at which these occurred (t_{max}), elimination half-life after patch removal and $AUC_{(0-\infty)}$ were similar in both groups.

Table 1 Mean (SEM) pharmacokinetic values after transdermal fentanyl application. Half-time represents time for plasma concentration to increase by 100% following patch application (see text for details of calculations). $t_{1/2}$ represents time for plasma concentration to decrease by 50% following patch removal
$^*p < 0.005$, unpaired *t* test.

	Young	Elderly
t_{max} (h)	24.5 (3.4)	28.1 (4.3)
c_{max} (ng ml^{-1})	1.9 (0.3)	1.5 (0.2)
Half-time (h)	4.2 (0.6)	11.1* (1.9)
$AUC_{(0-\infty)}$ (ng h^{-1} ml^{-1})	115 (19)	112 (22)
$t_{1/2}$ (h)	21.2 (2.8)	30.5 (6.4)

Discussion

After perioperative administration of transdermal fentanyl, plasma concentration profiles, efficacy and side effects were broadly similar in both elderly and younger patients, with similar calculated values to previous work.[6-8] Plasma concentrations increased to a plateau several hours after application and decreased slowly following patch removal. The prolonged half-life after patch removal may represent continued absorption from cutaneous depots of drug.[2] The mean maximum plasma concentration (c_{max}), time taken to achieve this (t_{max}), fentanyl half-life after patch removal ($t_{1/2}$) and $AUC_{(0-\infty)}$ did not differ significantly between the two groups. Values for clearance have not been presented as the bioavailability in this study is not known and absorption is likely to continue after patch removal. In common with many kinetic studies, the power of these data is low and the possibility of a type 2 error cannot be discounted. However, the time for plasma concentrations to double (half-time) was significantly greater in the

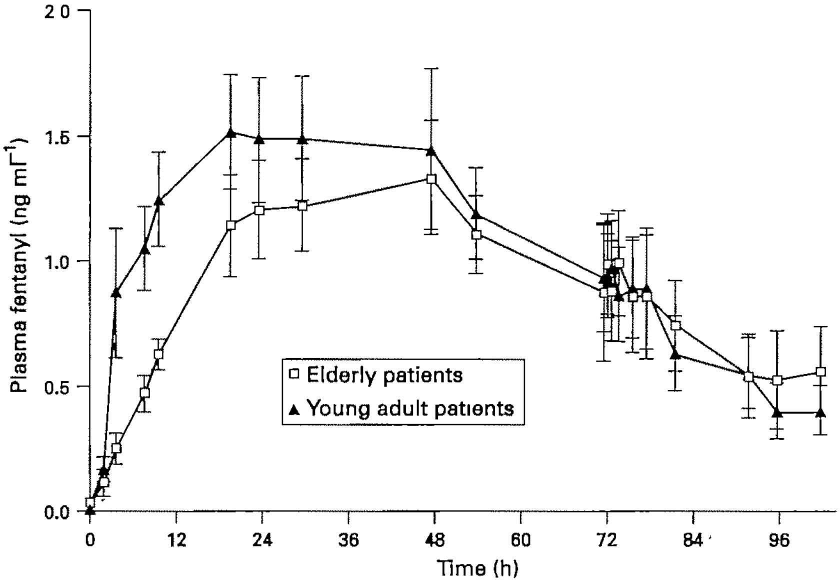

Figure 1 Mean (SEM) plasma fentanyl concentrations *vs* time after transdermal fentanyl patch application in elderly and young adult patients. Patches were removed at 72 h.

elderly. This may be related to alterations in skin perfusion, which is influenced by changes in temperature, circulating volume and cardiac output. All of these are likely to fluctuate in the perioperative period.

Previous studies investigating the pharmacokinetics of fentanyl in the elderly have produced conflicting results. Bentley and coworkers showed that i.v. fentanyl administration was associated with a higher peak plasma concentration, decreased clearance and increased elimination half-life in four elderly patients compared with five younger adult patients, although the calculated elimination half-lives for the elderly were outside the sampling period.[3] In contrast, Singleton and colleagues, studying younger (aged 18–41 yr) and elderly (aged 71–82 yr) patients after non-abdominal surgery found that although peak plasma concentrations were higher, and volume of distribution at steady state smaller in the elderly patients, clearance, elimination half-life and mean residence times were similar.[9] Although these studies relate to i.v. fentanyl, Duthie and colleagues[4] measured the plasma concentrations of fentanyl achieved following transdermal and i.v. fentanyl systems, both set to deliver 100 $\mu g\ h^{-1}$, after an initial i.v. bolus of 100 or 200 μg. There was no difference in plasma concentrations of fentanyl between the groups given 100 μg boluses from 8–24 h after the start of administration, suggesting that the application of transdermal fentanyl is associated with comparable therapeutic plasma concentrations. This has been borne out by other studies.[8–11] In doses of 25–125 $\mu g\ h^{-1}$, transdermal fentanyl can produce a significant opioid-sparing effect in patients after major abdominal or gynaecological surgery.[8–11] However, the incidence of nausea was 67–90% in patients receiving transdermal fentanyl.[8–10] These studies also documented a wide variation in the plasma fentanyl concentrations attained.

An incidence of respiratory depression of 11% has been demonstrated using transdermal fentanyl 50–75 $\mu g\ h^{-1}$ as a supplementary postoperative analgesic.[6] In our study, of the two elderly patients who experienced respiratory depression, one patient had a relatively low plasma concentration at the time (0.645 ng ml^{-1}) but had administered a large dose of morphine via the PCA. The other patient had a plasma concentration of 2.22 ng ml^{-1}, which is high in comparison with other patients in this and other studies. Although increased sensitivity to the depressant effects of opioids in the elderly is well established, the occurrence of respiratory depression with this dose of transdermal fentanyl is of concern, in particular as respiratory rate may not be a reliable indicator of respiratory depression at therapeutic plasma concentrations.[12]

In the one study of the effects of age on the kinetics of transdermal fentanyl, elderly and younger healthy adult volunteers wore a patch designed to deliver fentanyl 40 $\mu g\ h^{-1}$.[13] All of the 10 elderly subjects had the patch removed less than 24 h after application, because of respiratory depression or arterial desaturation in six and/or nausea and vomiting in nine subjects. When the serum concentrations were calculated with respect to the limited duration in the elderly group, they were higher than for the younger subjects, and altered absorption in the elderly was cited as the reason. The higher incidence of side effects, in particular respiratory depression, may relate to the use of volunteers, with no ongoing painful stimulus. A different pharmaceutical preparation was used, and patches were applied for a mean duration of 11 h in the elderly group,[13] so no further comparisons with our data have been made.

In summary, following transdermal fentanyl administration in the perioperative setting, the increase in plasma fentanyl concentrations was slower in the elderly patients. The incidence of respiratory depression confirms the view that transdermal fentanyl is not suitable for postoperative pain management in opioid-naive patients. When patients present for surgery with transdermal patches in place, the possibility of respiratory depression and variabilities in absorption should be considered.

Acknowledgements

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Effects of 1 MAC desflurane on cerebral metabolism, blood flow and carbon dioxide reactivity in humans

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Summary

We investigated the cerebral haemodynamic effects of 1 MAC desflurane anaesthesia in nine male patients scheduled for elective coronary bypass grafting. For the measurement of cerebral blood flow (CBF) a modified Kety-Schmidt saturation technique with argon as inert tracer gas was used. Measurements of CBF were made before induction of anaesthesia and 30 min after induction under normocapnic, hypocapnic and hypercapnic conditions in sequence. Changes in mean arterial pressure after induction of anaesthesia and during the course of the study were minimized using norepinephrine infusion. In comparison with the awake state under normocapnic conditions, desflurane reduced mean cerebral metabolic rate of oxygen ($CMRO_2$) by 51% and mean cerebral metabolic rate of glucose (CMRglc) by 35%. Concomitantly, CBF was significantly reduced by 22%; jugular venous oxygen saturation (Sjv_{O_2}) increased from 58 to 74%. Hypo- and hypercapnia caused a 22% decrease and a 178% increase in CBF, respectively. These findings may be interpreted as the result of two opposing mechanisms: cerebral vasoconstriction induced by a reduction of cerebral metabolism and a direct vasodilator effect of desflurane. CBF alterations under variation of Pa_{CO_2} indicate that cerebrovascular carbon dioxide reactivity is not impaired by application of 1 MAC desflurane. (*Br. J. Anaesth.* 1998; **81**: 155–160)

Keywords: anaesthetics volatile, desflurane; brain, metabolism; brain, blood flow; brain, carbon dioxide reactivity

The pharmacokinetic properties of desflurane may be of major advantage for anaesthesia in neurosurgical procedures, as early neurological examination after the emergence period may be desirable. Thus, substantial information on the cerebral effects of this agent is required and may be of clinical importance.

The effects of desflurane on cerebral metabolism and haemodynamics have already been studied in animals. In these experimental settings, desflurane caused a dose-dependent decrease in cerebrovascular resistance, an accompanying increase in cerebral blood flow (CBF) and a significant decrease in the cerebral metabolic rate of oxygen ($CMRO_2$). Cerebral vasculature remained responsive to changes in Pa_{CO_2} at 0, 5–1, 5 MAC desflurane, even in the presence of moderate hypotension.[1-3]

However, few investigations have been performed in humans.[4-7] Results from these studies are inconsistent with respect to carbon dioxide reactivity of CBF. Data on cerebral metabolism are lacking and the cerebral consequences of desflurane in patients with unimpaired cerebral circulation are presently unknown.

Therefore, this study was designed to investigate the cerebral haemodynamic and metabolic effects of desflurane anaesthesia in patients without evidence of neurological or cerebrovascular disease.

Patients and methods

Nine male patients scheduled for elective coronary bypass grafting were included in the study. After approval by the local Ethical Committee, written informed consent was obtained from each patient. According to clinical examination and duplex-ultrasonic investigation of intra-extra cranial arteries none of the patients showed evidence of cerebrovascular disease. Patients with a history or laboratory evidence of hepatic, renal, central or peripheral nervous disease or long-term misuse of drugs were excluded from the study. None of the patients had received general anaesthesia within 30 days of surgery. Cardiac medication was continued until surgery and premedication consisted of flunitrazepam 2 mg by mouth on the evening before and the morning of the surgical procedure.

CATHETERIZATION PROCEDURE

Before induction of anaesthesia, routine haemodynamic monitoring was established and included electrocardiography (leads II and V_5) and arterial, central venous, and pulmonary arterial catheterization. The pressure line of the arterial catheter was replaced by a gas-tight catheter (6-French gauge, Goodale Lubin, USCI, CR Bard, Billerica, MA, USA). In addition, a jugular bulb catheter of the same size was inserted by retrograde cannulation of the right internal jugular vein and the correct position was controlled by fluoroscopy.

INDUCTION AND MAINTENANCE OF ANAESTHESIA

I.v. etomidate 0.3 mg kg^{-1} was given, followed by incremental concentrations of desflurane in oxygen

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using face-mask ventilation. Vecuronium 0.1 mg kg^{-1} was administered to facilitate tracheal intubation. After intubation, 1 MAC desflurane (6 vol%) was administered constantly without supplementary doses of hypnotics or analgesics throughout the study period. Additional doses of vecuronium were administered when necessary.

Patients' lungs were mechanically ventilated using a volume controlled ventilator (Cato, Dräger AG, Lübeck, Germany). A positive end-expiratory pressure of 5 mm Hg was applied in all patients. Desflurane was administered by a Devapor vaporizer (Dräger AG, Lübeck, Germany) mounted on the ventilator. Delivery of desflurane was achieved through a semi-open circuit with a gas flow rate of 6 litre min^{-1} at a FI_{O_2} 0.3. The inspiratory and expiratory concentration of desflurane and other respiratory gases were continuously monitored with an integrated infrared absorption spectrometer (PM 8050 cd, Dräger AG, Lübeck, Germany).

After induction of anaesthesia norepinephrine was administered continuously in order to keep mean arterial pressure constant when compared with control values. To prevent hypothermia, a forced-air warming device (Warm Touch, Mallinckrodt, USA) with a whole body blanket was applied before induction of anaesthesia and during the complete period of measurements.

STUDY PERIOD

Measurements were made in the awake, premedicated patient before induction of anaesthesia (I); these values were considered as baseline. The following measurements were made in sequence after intervals of at least 30 min after induction under normocapnic conditions with Pa_{CO_2} about 5.3 kPa (II), under hypocapnic conditions with Pa_{CO_2} about 4.0 kPa (III) and under hypercapnia with Pa_{CO_2}=6.7 kPa (IV). The different levels of Pa_{CO_2} were achieved by adjusting the tidal volume of the ventilator inducing normo-, hyper- or hypoventilation, respectively.

At each measurement arterial, central venous, pulmonary capillary wedge and jugular bulb pressures were recorded on an eight-channel chart recorder; thermodilution measurements of cardiac output were taken at three random times during the respiratory cycle (Polymed CO computer, System 1281, Siemens, Munich, Germany).

TECHNIQUE OF CEREBRAL BLOOD FLOW MEASUREMENT

Cerebral blood flow was measured using a modified Kety-Schmidt inert gas saturation technique. Argon was used as the inert tracer gas.[8] A prepared gas mixture containing 70% argon and 30% oxygen was administered to the awake patient via a tight-fitting face mask and to the anaesthetized patient via the tracheal tube. During a 10 min wash-in period, blood samples from the arterial and the jugular bulb catheter were obtained simultaneously in duplicate at a constant rate by use of a high-precision aspiration pump (Braun Melsungen, Germany). The catheters had an identical deadspace and were known to exhibit only minimal loss of inert gas by diffusion. The determination of argon concentrations in arterial and cerebral venous blood samples were carried out by gas chromatography in triplicate.[9] A brain-blood partition coefficient of 1.10 was used for calculation of CBF.

Blood samples for measurements of electrolyte concentrations (Nova Electrolyte Analyser 1, Nova Biomedical, Waltham, MA, USA), blood glucose level (standard test combination, Boehringer Mannheim, Mannheim, Germany), oxygen saturation and haemoglobin content (CO-Oximeter Typ IL 282, Rotron Manufacturing, Woodstock, NY, USA) and oxygen and carbon dioxide tension (ABL 3, Radiometer, Kopenhagen, Denmark) were obtained twice, at the beginning and the end of each argon wash-in period. Cerebral metabolic rate of oxygen ($CMRO_2$) and glucose (CMRglc) were calculated as the product of CBF and the respective arterial cerebrovenous content difference.

The relationship between pooled CBF and Pa_{CO_2} data was described by a monoexponential function ($y=ae^{bx}$) using a non-linear fitting procedure (SigmaPlot 1.02 Jandel Scientific).

STATISTICAL ANALYSIS

All results presented in tables and figures are expressed as mean values (SD). Statistical analysis was performed by one-way analysis of variance and subsequent paired Student's *t* tests to compare the mean haemodynamic and metabolic variables between consecutive measurements. Because multiple tests were necessary to assess the time course of each variable, the level of significance (α=0.05) was adjusted by a sequentially rejective multiple test procedure according to Holm.[10]

Results

Measurements were made in all nine patients, but data from three patients under hypercapnic conditions (IV) had to be excluded because of technical difficulties. Mean age of the patients was 60 yr (range 47–68 yr), their mean body weight was 81.2 (10.8) kg and the mean height was 172 (3) cm. Metabolic and haemodynamic data are presented in table 1. Haemoglobin content was constant throughout the period of measurements and body temperature only minimally decreased after induction by 0.3 to 0.5°C. In accordance with the design of the study, arterial P_{CO_2} values did not differ between the control period (I) and normocapnia (II). Mean arterial P_{CO_2} during hypo- and hypercapnia was 3.9 (0.3) and 7.2 (0.5) kPa, respectively. Despite the administration of norepinephrine a 12% decrease in MAP occurred after induction of anaesthesia.

The application of 1 MAC desflurane induced a reduction of $CMRO_2$ compared with control values (I). Data obtained under normocapnic anaesthesia (II) showed a significant decline from 3.3 (0.7) to 1.6 (0.2) ml min^{-1} 100 g^{-1}. Hypocapnia (III) and hypercapnia (IV) produced a reduction to 2.1 (0.4) and 2.2 (0.6) ml min^{-1} 100 g^{-1}, respectively (fig. 1). Desflurane reduced the metabolic rate of glucose (CMRglc) significantly from 4.0 (0.7) to 2.6 (0.8) mg min^{-1} 100 g^{-1} under normocapnia (II) and also produced a decline to 2.4 (0.9) and 3.6 (2.6) mg min^{-1} 100 g^{-1} under hypocapnic (III) and hypercapnic (IV) conditions, respectively. CBF significantly decreased from 45 (10) ml min^{-1} 100 g^{-1}

Table 1 Mean (SD) metabolic and haemodynamic data of nine male patients. Study periods were: I=baseline=awake, before induction; II=normocapnia under 1 MAC desflurane 30 min after induction; III=hypocapnia under 1 MAC desflurane; IV=hypercapnia under 1 MAC desflurane; $CMRO_2$=cerebral metabolic rate for oxygen; CMRglc=cerebral metabolic rate for glucose; CBF=cerebral blood flow; Sjv_{O_2}=oxygen saturation in jugular bulb; Sa_{O_2}=arterial oxygen saturation; ajvDO2= arterio-jugular venous oxygen content difference; JBP=jugular bulb pressure, MAP=mean arterial pressure; CI=cardiac index; SVR=systemic vascular resistance; Pa_{CO_2}=arterial P_{CO_2}; Pa_{O_2}=arterial P_{O_2}; pHa=arterial pH; pHjv=jugular venous pH; Hb=haemoglobin concentration; Temp.=urine bladder temperature. Significant differences *=$P<0.05$ compared with baseline measurement (I)

		I *n*=9	II *n*=9	III *n*=9	IV *n*=6
$CMRO_2$	(ml min^{-1} $100g^{-1}$)	3.3 (0.7)	1.6 (0.2)*	2.1 (0.4)*	2.2 (0.6)*
CMRglc	(mg min^{-1} $100g^{-1}$)	4.0 (0.7)	2.6 (0.8)*	2.4 (0.9)*	3.6 (2.6)
CBF	(ml min^{-1} $100g^{-1}$)	45 (10)	35 (6)*	24 (4)*	125 (55)*
Sjv_{O_2}	(%)	58.4 (5.8)	74.2 (5.8)*	53.0 (8.8)	88.3 (2.3)*
Sa_{O_2}	(%)	96.6 (0.8)	98.4 (0.4)*	98.7 (0.3)*	97.6 (1.1)
$ajvDO_2$	(ml 100·ml^{-1})	7.6 (1.0)	4.7 (1.0)*	8.8 (1.6)	1.9 (0.5)*
JBP	(mm Hg)	6 (1)	9 (3)*	9 (2)*	9 (6)
MAP	(mm Hg)	91 (11)	79 (10)*	86 (12)	92 (14)
CI	(litre min^{-1})	2.7 (0.4)	2.7 (0.6)	2.6 (0.5)	3.6 (0.7)*
SVR	(dyn s^{-1} cm^{-5})	1343 (248)	1133 (281)	1296 (329)	1045 (321)
Pa_{CO_2}	(kPa)	5.6 (0.5)	5.5 (0.3)	3.9 (0.3)*	7.2 (0.5)*
Pa_{O_2}	(kPa)	12.0 (1.2)	18.7 (4.6)*	18.5 (4.3)*	19.6 (5.5)*
pHa		7.43 (0.03)	7.41 (0.02)	7.52 (0.02)*	7.33 (0.03)*
pHjv		7.37 (0.03)	7.37 (0.02)	7.44 (0.02)*	7.31 (0.03)*
Hb	(g dl^{-1})	14.3 (1.1)	14.0 (1.5)	14.0 (1.7)	14.2 (1.0)
Temp.	(°C)	35.9 (0.3)	35.4 (0.6)*	35.4 (0.7)*	35.6 (0.3)*

during the control period (I) to 35 (6) after the application of 1 MAC desflurane (II). Hypocapnia (III) induced a further decrease in CBF to 24 (4) ml min^{-1} 100 g^{-1} and hypercapnia (IV) a major increase to 125 (55) ml min^{-1} 100 g^{-1} (fig. 2). 1 MAC desflurane anaesthesia increased cerebral venous oxygen saturation (Sjv_{O_2}) from a mean value of 58% in the awake state (I) to a mean of 74% under normocapnic conditions (II) (fig. 3). Cerebrovascular carbon dioxide reactivity showed no impairment under the administration of 1 MAC desflurane. In the range of Pa_{CO_2}, the relationship between CBF and Pa_{CO_2} could best be described by the monoexponential function $y=4.29e^{0.442x}$ (fig. 4).

Discussion

Desflurane leads to a disproportionate decrease in CBF and metabolism resulting in a significant increase in jugular venous oxygen saturation. At the same time, however, 1 MAC desflurane preserves cerebrovascular carbon dioxide reactivity.

METHODOLOGICAL CONSIDERATIONS

For ethical reasons, patients in this clinical study received flunitrazepam for oral premedication, which we believe to be indispensable for patients suffering from coronary artery disease. Benzodiazepines, however are known to have mild cerebral vascular effects[11 12] and may thus have interfered with desflurane-induced changes in CBF and $CMRO_2$. As baseline measurements in our study were performed in premedicated patients, comparable conditions applied for all measurements and this additional pharmacological effect seems unlikely to have influenced the changes in cerebral haemodynamics. Similarly, induction of anaesthesia with etomidate preceded maintenance with desflurane. Etomidate is also known to reduce CBF and $CMRO_2$ in humans.[13 14] The pharmacokinetic properties of etomidate, however, indicate that plasma concentrations after an induction dose decrease below the therapeutic range 5 min after application.[15 16] We therefore considered a 30-min period after induction of anaesthesia safe enough to exclude major interference of etomidate with the effects of desflurane on cerebral circulation.

Desflurane anaesthesia may reduce mean arterial pressure because of a decrease in systemic vascular resistance.[17] Norepinephrine was thus infused after induction of anaesthesia to prevent major changes in cerebral perfusion pressure and to minimize additional cerebral haemodynamic effects because of autoregulation of CBF. This additional pharmacological intervention is unlikely to have caused direct cerebral vascular or metabolic effects because application of $alpha_1$-agonists are known to have little or no direct effect on CBF in humans as long as the blood–brain barrier is intact.[18 19] Unfortunately, mean MAP slightly decreased after induction of anaesthesia despite norepinephrine administration. The resulting reduction in cerebral perfusion pressure thus has to be considered in the interpretation of changes associated with 1 MAC desflurane anaesthesia.

The Kety-Schmidt technique is widely accepted as a reference method for measurements of global CBF and cerebral metabolism.[20 21] In this study mean CBF during the baseline period in awake patients was 45 (10) ml min^{-1} 100 g^{-1} which is slightly lower than global CBF values found by Madsen and co-workers at corresponding Pa_{CO_2} levels.[22] This small difference, however, is probably caused by the effect of pre-anaesthetic benzodiazepine administration rather than by methodological differences. Our data are in close agreement with a clinical study by Weyland and co-workers, who investigated the time course of global CBF in cardiac surgical patients.[23] The baseline values of $CMRO_2$ we report here are similar to normal values found in previous investigations.[24 25]

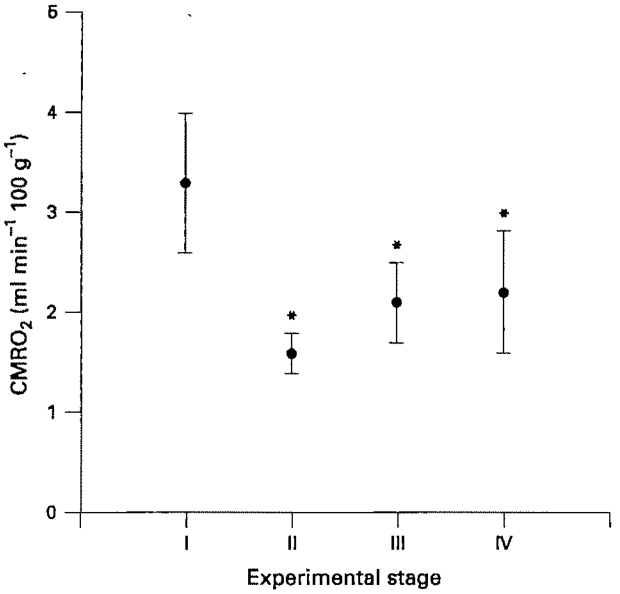

Figure 1 Mean (SD) changes of cerebral metabolic rate of oxygen ($CMRO_2$). I=awake; II=normocapnia under 1 MAC desflurane 30 min after induction; III=hypocapnia; IV=hypercapnia. *Significant difference from awake measurement (I). $P<0.05$.

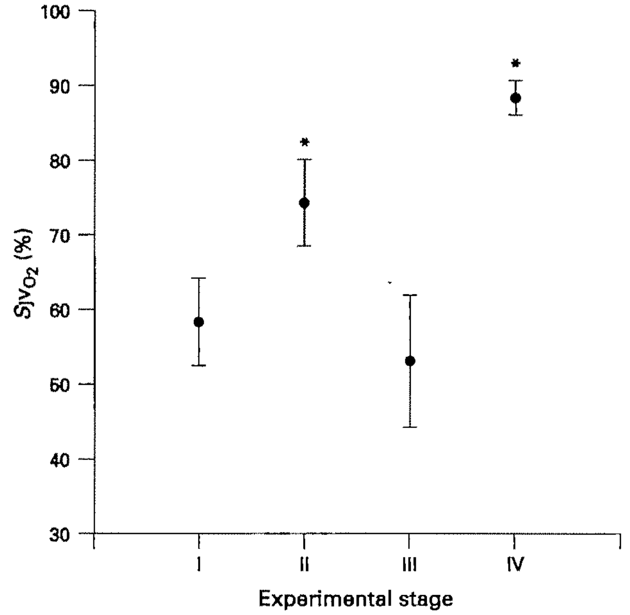

Figure 3 Mean (SD) changes of jugular venous oxygen saturation (Sjv_{O_2}). I=awake; II=normocapnia under 1 MAC desflurane 30 min after induction; III=hypocapnia; IV=hypercapnia. *Significant difference from awake measurement (I). $P<0.05$.

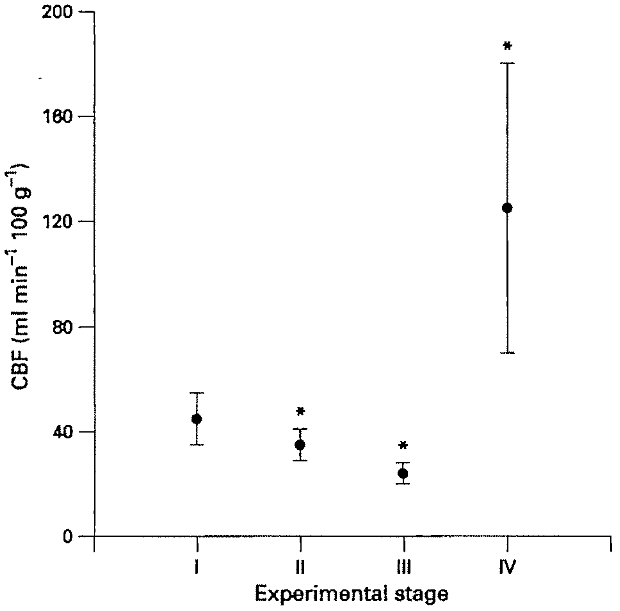

Figure 2 Mean (SD) changes of cerebral blood flow (CBF). I=awake; II=normocapnia under 1 MAC desflurane 30 min after induction; III=hypocapnia; IV=hypercapnia. *Significant difference from awake measurement (I). $P<0.05$.

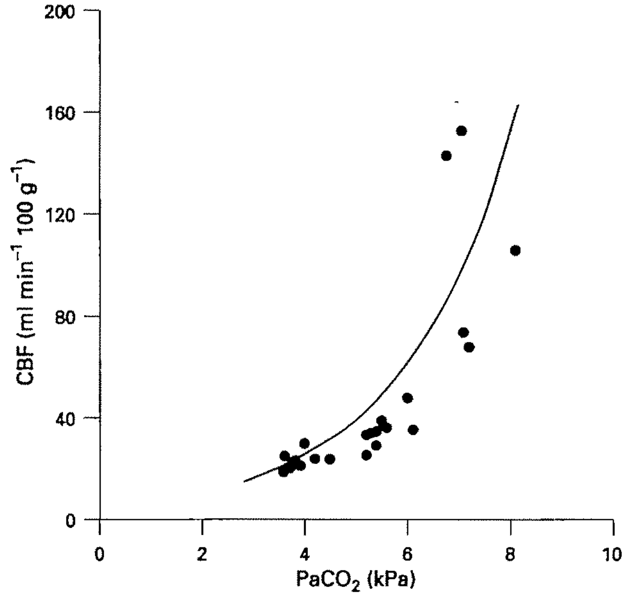

Figure 4 Relationship between cerebral blood flow (CBF) and arterial carbon dioxide pressure (Pa_{CO_2}) under 1 MAC desflurane anaesthesia. All measurements II - IV were included for evaluation. $y=4.29e^{0.442x}$ with $n=24$.

CEREBRAL METABOLISM

Administration of potent inhalation anaesthetics is known to reduce cerebral metabolism in a dose-dependent manner in animals as well as in humans. These data on the effect of 1 MAC desflurane are generally in agreement with findings on the effects of other inhalation anaesthetics. However, the reduction in $CMRO_2$ by 51% is greater than expected from previous clinical studies on the cerebral effects of other inhalation anaesthetics. The reduction in $CMRO_2$ is in line with comparable data from an experimental investigation in cats showing a 45% reduction in $CMRO_2$ after application of 1 MAC isoflurane when compared with a control group of animals under nitrous oxide anaesthesia.[26] As expected, the cerebral metabolic rate for glucose was also significantly reduced, but slightly less than was $CMRO_2$. In principle the resulting change in the oxygen-glucose index of the brain might suggest a change in metabolic substrates or pathways. The difference between the relative change in $CMRO_2$ and CMRglc, however, is well within the range found in other investigations on cerebral metabolism under different anaesthetics.

In analogy to the effects of most other anaesthetics it can be assumed that the reduction in cerebral metabolism was caused primarily by the reduction in cerebral activity associated with the anaesthetic effect of desflurane; an intrinsic effect on cellular metabolism seems unlikely at a concentration of 1 MAC. Other inhalation anaesthetics, such as halothane, do not decrease cerebral metabolism when used as a supplement to deep i.v. anaesthesia.[27]

CEREBRAL BLOOD FLOW

Administration of 1 MAC desflurane caused a reduction of CBF by 22%, although Pa_{CO_2} remained unchanged. Until now, comparable data from humans are lacking. Results from a clinical investigation by Ornstein and co-workers[5] lack comparability, as measurements were obtained with the i.v. ^{133}xenon method and MAP was not stabilized. Furthermore, patients suffered from intracranial mass lesions and control measurements differed from this study, with CBF measured at three concentrations (1.0, 1.25 and 1.5 MAC) of desflurane under mild and moderate hypocarbia. The reduction of global cerebral metabolism and CBF after administration of desflurane suggests a preservation of coupling between metabolism and blood flow. In this study the 22% decrease in mean CBF, however, was disproportionate when compared with the reduction in $CMRO_2$ and CMRglc. This finding explains the observed increase in cerebral venous oxygen saturation and suggests a direct cerebral vasodilatory effect which partially counteracts the decrease in CBF associated with the reduction in cerebral metabolism. This hypothesis is supported by a recent investigation by Matta, Mayberg and Lam[28] who uncoupled the cerebral metabolic and vascular effects of desflurane by simultaneous propofol anaesthesia and demonstrated the direct cerebral vasodilatation during preexistent EEG silence under clinical conditions using a phenylephrine infusion to maintain MAP. Their results also support findings from an animal study,[1] which also showed a slight decrease in CBF during desflurane anaesthesia that most probably can be understood as the result of two opposing mechanisms: cerebral vasoconstriction caused by a reduction in cerebral metabolism and a direct vasodilator effect of desflurane.

In our patients, the understanding of the cerebral haemodynamic effects of desflurane is further complicated by a slight decrease in mean arterial pressure which occurred despite administration of norepinephrine and unchanged cardiac index. It therefore cannot be excluded that the mild reduction in global CBF also occurred as a consequence of the decrease in cerebral perfusion pressure and impaired autoregulation of blood flow. This, however, seems unlikely as the stable cerebral vascular resistance suggests that the vasodilatory effect of desflurane was completely counterbalanced by a metabolically-induced reduction in CBF and thus would not explain the significant increase in cerebral venous oxygen saturation. Although recent data obtained by transcranial Doppler sonography indicate that autoregulation of CBF might be impaired at higher desflurane concentrations,[6] previous studies in patients with intracranial mass lesions demonstrated preservation of cerebral vascular autoregulation.[5]

Hypercapnia induces cerebral vasodilatation resulting in increased CBF. As it is well known that Pa_{CO_2} and CBF have an exponential relationship, hyper-perfusion in this setting must be regarded as drug-related effect. Overestimation of CBF for methodological reasons seems unlikely as $CMRO_2$ (as a product of CBF and $ajvDO_2$) during hypercapnia remained constant when compared with hypo- and normocapnia, respectively.

In this study Sjv_{O_2} values during baseline conditions and hypocapnia might be a matter of concern. Jugular venous oxygen saturation of the sedated, non-ventilated patients (I) was significantly lower than under normocapnic anaesthesia. Under preexistent arterial normoxaemia benzodiazepine premedication probably causes a disproportionate minor reduction in CBF compared with cerebral metabolism and therefore contributes to the reduced oxygen saturation in the jugular bulb. An even lower jugular oxygen saturation was measured under hypocapnic anaesthesia (III). Under good arterial oxygen saturation, hypocapnia reveals a situation that has to be understood as an ischaemic threat, at least to the damaged brain and should be used with considerable care.

Futhermore, our results show that changes in CBF in response to variations of Pa_{CO_2} are comparable to respective changes in human volunteers,[29] indicating that cerebral vascular carbon dioxide reactivity is not impaired by administration of 1 MAC desflurane.

In summary, we conclude that in patients without evidence of cerebral vascular disease 1 MAC desflurane anaesthesia causes a decrease in global CBF as a consequence of a pronounced reduction in cerebral metabolism. These haemodynamic effects of changes in cerebral metabolism are partially counterbalanced by an intrinsic cerebral vasodilatory effect of desflurane which causes a reduction in cerebral oxygen extraction, but does not impair cerebral vascular carbon dioxide reactivity.

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Model for the administration of low-flow anaesthesia

D. M. BEAMS, F. J. SASSE, J. G. WEBSTER AND R. G. RADWIN

Summary

A general (multiple-gas) three-compartment mass-balance model of the circle–absorber breathing circuit with intermittent positive-pressure ventilation has been developed. We propose it as a tool to determine flowmeter and vapourizer settings for inhalation anaesthesia by low-flow methods (less than 1 litre min^{-1} total fresh gas flow). This model reproduces the results of various previously-published mass-balance models, but it appears to underestimate slightly the delivery of fresh gases to the inspired limb of the breathing circuit when tested with clinical data from surgical cases. Low-flow dosing schedules for 35% inspired oxygen and 1% inspired halothane were computed with the model and tested *in vitro* with a circle–absorber breathing circuit and an active gas-exchange lung at nine values of simulated patient gas exchanges. The mean inspired oxygen concentration over all trials was 32.8% (SD=1.9%), while the mean inspired halothane concentration was 1.2% (SD=0.3%). The flow meter and vapourizer settings calculated from the model appear to have sufficient accuracy to be useful in the clinical setting in conjunction with active oxygen and anaesthetic agent monitoring. (*Br. J. Anaesth.* 1998; **81**: 161–170)

Key words: equipment, breathing systems; model, numerical; anaesthesia, low-flow

Inhalation anaesthesia is administered with fresh-gas flows which often exceed patient gas requirements by a large margin. For example, total fresh gas flows of 2–3 litre min^{-1} are frequently used, while homeostasis of the breathing circuit with carbon dioxide absorption could in principle be maintained with fresh gas flows just equal to the patient gas requirements for oxygen and anaesthetic gases. There are practitioners who do advocate the use of such a completely closed-circuit technique (for example, Lowe and Ernst[1]) who cite as its advantages conservation of resources, an increased awareness on the part of the clinician for the physiological status of the patient,[1 2] and an increased awareness of the performance of the anaesthesia machine itself.[3] Closed-circuit technique, however, is labour-intensive. High fresh gas flows ensure that the inspired concentrations are essentially the same as the settings of the anaesthesia machine regardless of patient uptakes, simplifying the titration of inspired gases at the expense of wasted resources. Low-flow technique (<1 litre min^{-1} total fresh gas flow) is an alternative to both high-flow and closed-circuit techniques. Relative to high-flow technique, low-flow conserves patient body heat and humidity[4–10] and reduces costs[11–17] but differences between machine settings and inspired concentrations may be substantial when low flows are used.[18] We propose a model of the circle–absorber breathing circuit and patient as a tool to aid in the titration of inspired gases in low-flow anaesthesia. We first present the basic model; we then test its ability to duplicate results of other modelling studies and to explain clinical data. We conclude with *in vitro* experiments of dosing schedules derived from the model.

Structure of the mass-balance model

The structure of the model is shown in figure 1; the model incorporates three chambers (alveolar space, carbon dioxide absorber, and bellows; designated A, Ab, and B, respectively). The structure is explicitly that of a circle-absorber breathing circuit with intermittent positive-pressure ventilation. We assume that tidal gas flows may be replaced by equivalent continuous mean-valued flows and that mass balance in all three chambers must be simultaneously satisfied for carbon dioxide, nitrogen, nitrous oxide, oxygen, and anaesthetic agent vapour. Table 1 gives the nomenclature of the model. Detailed description of the model and its numerical solution are given in Appendix 1.

Methods

COMPARISON OF THE MASS BALANCE MODEL WITH PREVIOUS MODELS

Assessment of this general mass-balance model depends, in part, upon its ability to replicate the results of previous specific mass–balance models. We compared the model's relationship of alveolar carbon dioxide to alveolar ventilation to previously–published work. We also compared computed relationships between oxygen and carbon dioxide at various points in the circle–absorber system to previous work.

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Table 1 Summary of the nomenclature of figure 1

Symbol	Interpretation
V_F	Total fresh-gas flow
$\dot{V}_{FAb}$	Flow of fresh gas into CO_2 absorber
V_{FI}	Flow of fresh gas into inspiratory path
V_{AbB}	Flow leaving CO_2 absorber directed toward bellows
V'_{AbB}	Flow from CO_2 absorber reaching bellows
$\dot{V}_{BAb}$	Flow leaving bellows directed toward CO_2 absorber
$\dot{V}'_{BAb}$	Flow from bellows reaching CO_2 absorber
$V_{L_{BAb}}$	Leak from bellows-to-CO_2 absorber path
V_{AbI}	Flow from CO_2 absorber into inspiratory path
V_I	Inspiratory-path gas flow
$\dot{V}_{AI}$	Inspired alveolar ventilation
V_D	Deadspace/compliance shunt
$\dot{V}_{L_I}$	Leak of gas from inspiratory path
V_{Law}	Leak of gas at the patient airway connection
$\dot{V}_{AE}$	Expired alveolar ventilation
V_{L_E}	Leak of gas from expiratory path
V_E	Expiratory-path gas flow
$\dot{V}_{BS}$	Bellows-to-scavenging (spilt gas) flow
$k_{L_{BAb}}$	Apportioning parameter for bellows-to-CO_2 absorber leak
k_{Law}	Apportioning parameter for patient airway connection leak
F_F	Vector of fresh gas concentrations
F_{Ab}	Vector of CO_2 absorber gas concentrations
F_I	Vector of inspiratory concentrations
F_A	Vector of alveolar concentrations
F_E	Vector of expiratory concentrations
F_B	Vector of bellows concentrations

VALIDATION OF THE MODEL WITH CLINICAL DATA

Portable instrumentation depicted in figure 2 was developed to measure in the clinical setting the parameters required as inputs to the mass-balance model. Fresh gases pass through a laminar-flow element (Merriam Instruments, Cleveland, OH, USA), creating a differential pressure linearly proportional to flow; spilt gases pass through a second laminar-flow element. Differential pressures across the flow elements are converted to voltages by precision differential-pressure transducers. Calibrations for each flow element–pressure transducer pair were developed with a rotameter specified for air at 101.3 kPa and 21 °C. Electrically-operated poppet valves allow a Datex AGM–103 Capnomac respiratory-gas monitor with optional four-channel analogue output card (Datex Instrumentarium, Helsinki, Finland) to sequentially measure the fresh gas and spilt gas concentrations of oxygen, nitrous oxide, anaesthetic agent, and carbon dioxide. Gas concentration and temperature data (measured by thermistors) are used to correct the flow readings for viscosity. Our apparatus measures exchanges of oxygen, nitrous oxide, and anaesthetic agent as differences between the fresh gas and spilt gas mass flows. Carbon dioxide exchange could not be directly measured because of the presence of the absorber.

Gas flows in the limbs of the breathing circuit were converted to differential pressures by variable-orifice flow elements (Allied HealthCare, Riverside, CA, USA) placed between the carbon dioxide absorber (Ohmeda GMS) and the breathing-circuit hoses. Differential-pressure transducers converted the pressures to voltages. Each flow element and transducer pair was individually calibrated with air. A second Capnomac sequentially measured concentrations of gases in the limbs of the breathing circuit. A correction for gas density relative to air was computed from the limb concentration readings and applied to the measured flows. The exhaust of the Capnomac consists of a mixture of sampled gases and a small amount (typically 25–40 ml min^{-1}) of room air drawn as a reference for its paramagnetic oxygen sensor. The exhaust of the second Capnomac was not returned to the breathing circuit, but it did pass through the spilt-gas laminar-flow element. We measured the air flow of this instrument to determine the

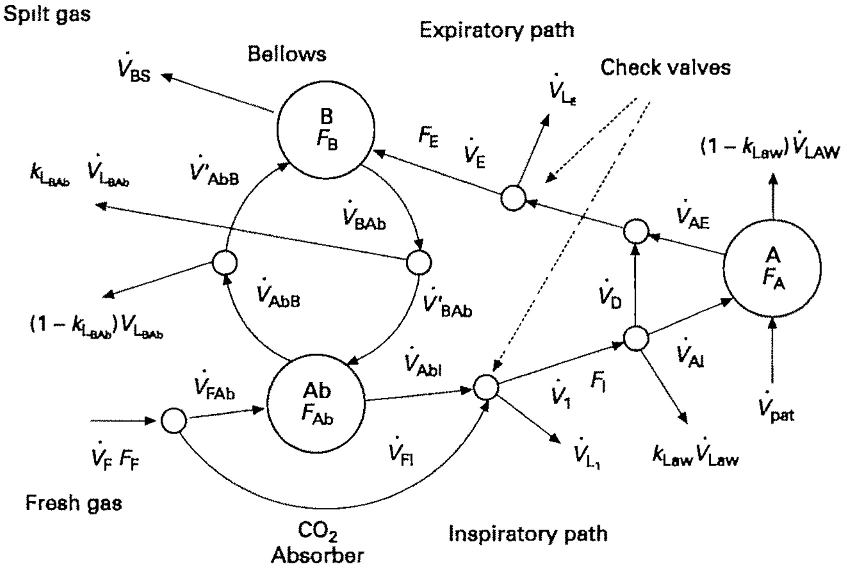


Figure 1 Mass-balance model of the patient and circle-absorber breathing circuit. Location of the check valves is shown for reference; that portion of the model to the left of the valves is the anaesthesia machine and that portion to the right is the breathing circuit and patient.

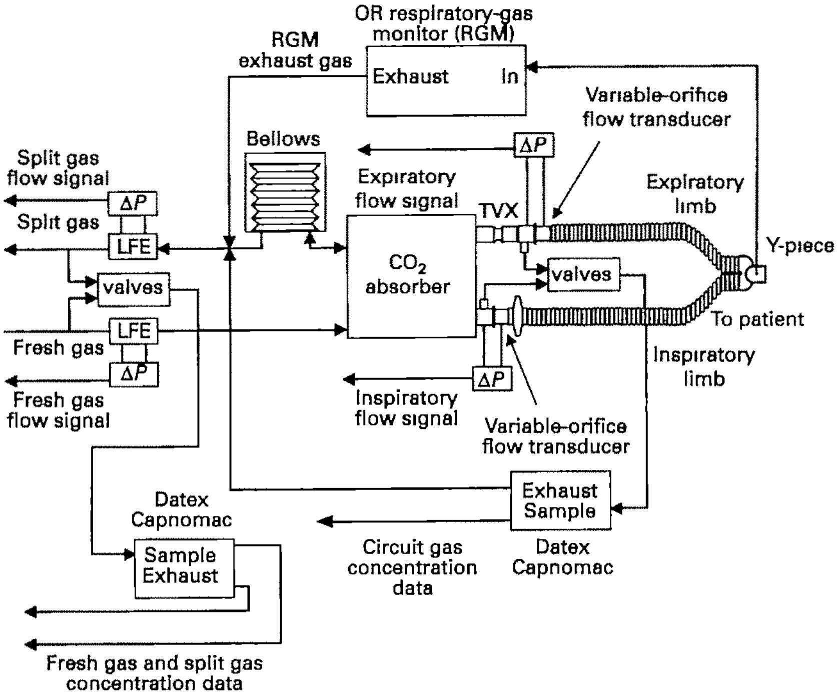


Figure 2 Apparatus used in the clinical portion of this study connected to the anaesthesia machine and breathing circuit. The labels 'LFE' indicate laminar-flow elements; the label 'TVX' represents an Ohmeda TVX turbine-type flow sensor which was present in all cases.

additional amounts of oxygen and nitrogen thus added to the spilt gases. The exhaust of the operating room respiratory gas monitor was also rerouted to pass through the spilt-gas laminar-flow element. Neither the Ohmeda 5250 RGM nor the Ohmeda Rascal II monitors encountered in this study contaminate their exhaust streams with room air.

Data were recorded with a portable PC and a Daqbook 200 16-channel data-acquisition system (IOtech, Cleveland, OH, USA). Data were taken at either a high rate (10 samples s^{-1}) or a low rate (one sample every 5 s). We followed a repetitive sequence of 5 min of high-rate data, 1 h of low-rate data, and a brief interval to zero the fresh-gas and spilt-gas flowmeters. High-rate data were used to determine the limb gas flows, respiratory rate, and durations of *I* and *E*. Low-rate data were used to determine patient gas exchanges. (The linear nature of the laminar-flow elements permits measurement of mean flows from the mean pressure-transducer output voltages, but the non-linear pressure *vs* flow relationship of the variable-orifice flow sensors precluded this for the limb gas flows.) Data-taking commenced with the start of mechanical ventilation and continued throughout the case. Two additional segments of high-rate data were taken at the start of a case. Low-rate data taking was suspended and a new high-rate data section taken if the anaesthetist changed ventilatory parameters during the case. End-tidal carbon dioxide partial pressures were noted periodically. The electric valves preceding the Datex instruments were automatically switched after four breaths (high rate) or 16 breaths (low rate), determined from inspiratory flow. A complete epoch of high-rate data spanned eight breaths; an epoch of low-rate data comprised 32 breaths. We presumed that gas concentrations measured during one half of an epoch are applicable to the entire epoch.

Approval for the experimental procedure was granted by the institutional review board of the University of Wisconsin Center for Health Sciences under protocol number 96-320-099.

Table 2 summarizes the patient population. Various surgical procedures (such as abdominal, peripheral, vascular, and orthopaedic) are represented in the patient population. Anaesthesia was induced i.v. in all patients except for the paediatric patient when anaesthesia was induced by mask with sevoflurane. Anaesthesia was maintained by inhalation of isoflurane. All operating rooms used Ohmeda GMS carbon dioxide absorbers and Ohmeda 7000 or 7800 ventilators. A total of 169 epochs of low-rate data from 13 surgical cases were selected to apply to the model; Table 2 lists the number of epochs from each patient. Only those epochs in which the measured inspiratory and expiratory gas concentrations were constant and in which the sum of all gas fractional concentrations

Table 2 Summary of the surgical cases involved in clinical validation of the mass-balance model. The column labelled 'Balance gas' indicates whether nitrous oxide or air was administered with oxygen. One case involved a change in balance gas at approximately 150 min. The column labelled 'Data Epochs' indicates the number of useful data segments acquired from the case

Sex	Body mass (kg)	Age (yr)	Balance gas	Data epochs
M	84.8	68	N_2O	14
M	88.2	43	N_2O	22
M	60.5	26	N_2O	12
F	77	51	N_2O	26
F	65.2	44	N_2O	20
M	17	4	N_2O	15
F	60	36	Air	1
M	80	64	N_2O	3
M	81.4	78	Air	6
M	68	65	Air	3
M	67.9	22	N_2O/Air	10/10
F	68 8	56	N_2O	23
M	71.5	57	Air	4

(fresh gases, inspired and expired gases, and spilt gases) was 1.00±0.015 were used (this rule was not applied in cases in which air was used as a fresh gas). Ventilatory parameters for the model were measured from high-rate data. Carbon dioxide production by the patient was estimated at 0.8 times the measured oxygen consumption and the deadspace/compliance shunt value adjusted until the modelled end-tidal carbon dioxide matched the recorded value. Modelled inspired concentrations of oxygen, nitrous oxide, and isoflurane were computed for comparison with measured results.

TESTS OF LOW-FLOW DOSING SCHEDULES COMPUTED FROM THE MODEL

We tested model-derived low-flow dosing schedules in an *in vitro* experiment shown in figure 3. A circle–absorber system was supplied with oxygen and nitrous oxide metered through calibrated rotameters and halothane from a Fluotec 4 vapourizer (Ohmeda, Madison, WI, USA). The patient was simulated with an active gas-exchange lung. A Michigan Instruments Dual-Adult Test and Training Lung (Michigan Instruments, Grand Rapids, MI, USA) was modified by the addition of an exhaust port through which gases could be drawn from the lung into a vacuum scavenging system and a backfill port through which gases could be added to the lung. A thermal mass-flow controller regulated the constant flow of 2 litre min^{-1} through the exhaust port with computer correction for varying gas compositions (measured by a Datex Capnomac with four-channel analogue output card). The exhaust-port gases are replaced by fresh gases to produce apparent exchanges. For example, suppose the gases in the lung at a given moment contained 35% oxygen. The 2 litre min^{-1} exhaust flow would then extract 700 ml min^{-1} of oxygen from the lung. Let us suppose the commanded oxygen exchange was −240 ml min^{-1}; this would be achieved by introducing 460 ml min^{-1} of oxygen at the backfill port. Exchanges of other gases are similarly produced. The active lung is capable of producing apparent exchanges of oxygen, nitrogen, nitrous oxide, carbon dioxide, and a volatile anaesthetic agent.

Oxygen, halothane, and nitrous oxide exchanges of the lung were measured for nine separate combinations of nitrous oxide and halothane exchange settings with a constant oxygen exchange setting of 240 ml min^{-1}. These measurements were made for the isolated test lung. Dosing schedules to produce 35% inspired oxygen and 1% inspired halothane were computed for each set of measured exchanges by the procedure described in Appendix 2. The circle–absorber system was ventilated by an Ohmeda 7800 ventilator at 6 bpm with a tidal volume of 750 ml and an *I:E* ratio of 1:2. An initial period of high fresh gas flows (2 litre min^{-1} each of oxygen and nitrous oxide with a vapourizer setting of 1%) was used to drive the inspired concentrations to initial values of approximately 50% each of nitrous oxide and oxygen with 1% halothane. The rotameters and vapourizer were then adjusted to the low-flow dosing schedule corresponding to the particular set of lung gas exchanges. Inspired concentrations were read at intervals of 5 min for an hour of low-flow administration by a Datex Capnomac which was continuously attached to the inspiratory limb whose sampling flow was included in the model as an inspiratory leak when dosing schedules were computed.

Results

COMPARISON WITH PREVIOUS MASS-BALANCE MODELS

Alveolar ventilation $\dot{V}_{AI}$, alveolar carbon dioxide concentration $F_{A_{CO_2}}$, and the patient carbon dioxide

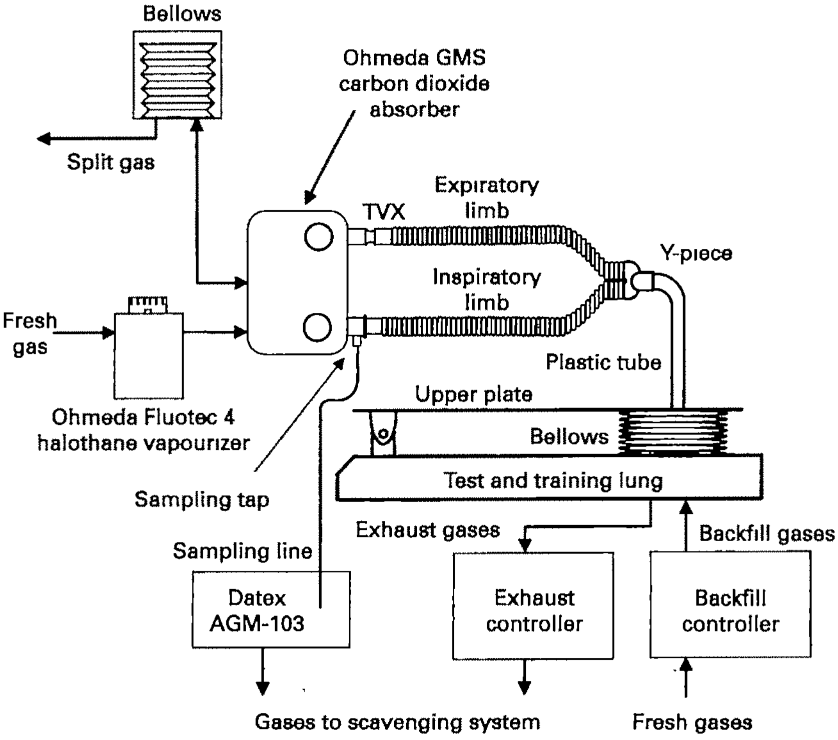


Figure 3 Apparatus used in the *in vitro* tests of dosing regimes derived from the model.

exchange $\dot{V}_{CO_2}$ are related by [19,20]:

$$F_{A_{CO_2}} = \frac{\dot{V}_{CO_2}}{\dot{V}_{AI}}$$

We found the mass-balance model to reproduce this relationship.

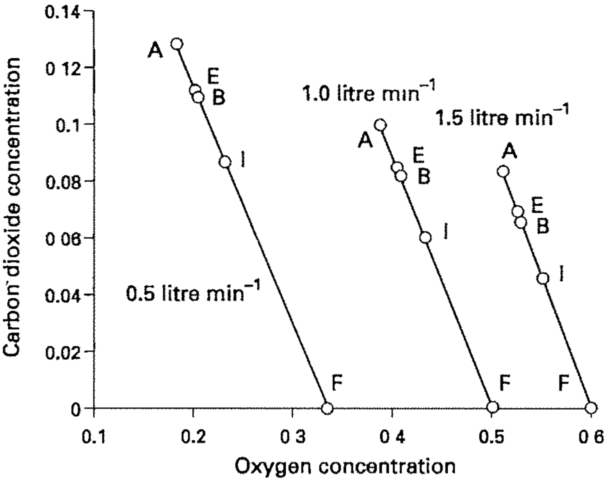
Oxygen–carbon dioxide relationships at various points in the circle-absorber system are described for systems without[21] and with[22] carbon dioxide absorption. Figure 4 depicts the oxygen–carbon dioxide diagram obtained with the mass-balance model without carbon dioxide absorption with fixed patient gas exchanges, fixed fresh nitrous oxide flow, and three values of fresh oxygen flow. The loci of an oxygen–carbon dioxide diagram such as figure 4 are straight lines whose slopes are given by[21]:

$$\frac{1}{\Delta} = -\left(F_{F_{O_2}} + \frac{1-F_{F_{O_2}}}{R}\right)$$

where Δ is the slope, $F_{F_{O_2}}$ is the fresh gas oxygen concentration, and R is the respiratory quotient. The model agrees with published results for circle-absorber systems both without carbon dioxide absorption[21] and with complete carbon dioxide absorption.[22]

RESULTS WITH CLINICAL DATA

Figures 5, 6, and 7 present modelled oxygen, nitrous oxide, and anaesthetic agent concentrations compared with their measured values. The model appears to slightly underestimate oxygen and agent concentrations and overestimate that of nitrous oxide. Table 3 gives a summary of inspired concentrations, including those for nitrogen from cases in which air was used. The model's nominal estimation error in inspired oxygen at a measured inspired concentration of 35% is –1.2% with a range of 0 to –2.2% ($P<0.05$); the mean estimation error in isoflurane at a measured inspired concentration of 1% is –0.09% with a range from 0.04% to –0.1% ($P<0.05$).



Oxygen flow, litre min^{-1}	Slope from eq 2	Slope from fig. 4
0 5	–0.857	–0 859
1.0	–0.889	–0 889
1 5	–0.909	–0.909

Figure 4 Carbon dioxide/oxygen diagram obtained from the mass-balance model under conditions of the fresh-gas oxygen flows specified on the diagram Data are labelled as follows: F, fresh gas, I, inspired gas; B, bellows (or split) gas; E, expired gas, and A, alveolar gas Model parameters used in this simulation were as follows: minute ventilation, 6 0 litre min^{-1}; *I:E* ratio, 1:2, deadspace ventilation, 2.5 litre min^{-1}; fresh gas flow, 1.0 litre min^{-1} of nitrous oxide in addition to the indicated flows of oxygen; patient carbon dioxide exchange, 160 ml min^{-1}; oxygen exchange, 200 ml min^{-1}; nitrous oxide exchange, 0 ml min^{-1}

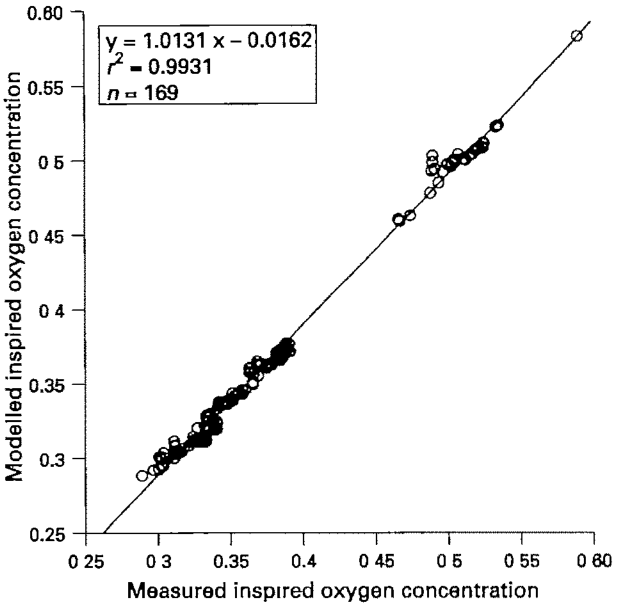


Figure 5 Modelled inspired fractional oxygen concentration compared with measured inspired oxygen concentration including the regression line and its defining equation. Measured inspired oxygen concentrations in the range of 0 3–0.4 occurred in cases in which nitrous oxide was administered; concentrations above 0.45 were typically from cases in which air was administered in conjunction with pure oxygen

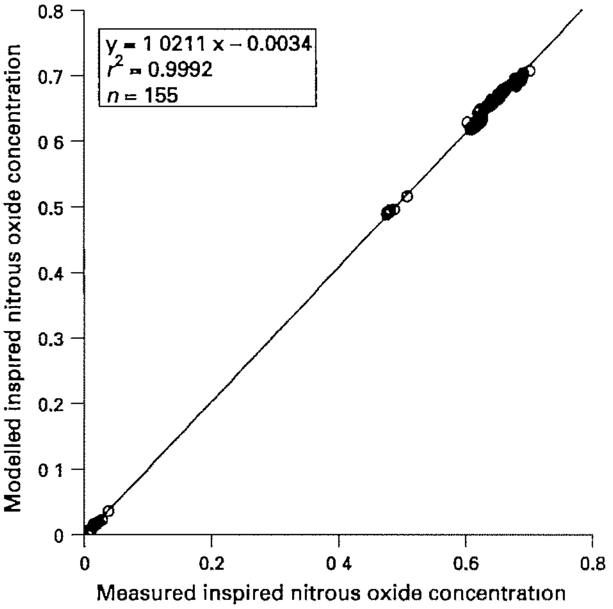


Figure 6 Modelled versus measured inspired fractional nitrous oxide concentrations Data showing measured concentrations under 0.10 were taken during the case of a 22-yr-old male patient during the period after nitrous oxide had been replaced by air. These low inspired concentrations were the result of washout of circuit nitrous oxide and continued excretion of nitrous oxide by the patient.

Table 3 Linear regressions relating inspired gas concentrations computed by the model to measured inspired gas concentrations. Parameters Max slope, Min slope, Max intercept, and Min intercept represent the joint confidence interval of the regression slope and intercept to a 95% confidence level. The computed values of the *f*-statistic demonstrate significance of the regressions ($P<0.01$)

Parameter	Oxygen	Nitrous oxide	Nitrogen	Isoflurane
Slope	1.0131	1.0211	0.9045	0.9343
Intercept	–0.0162	–0.0034	0.0543	0.0002
n	169	155	24	169
r^2	0.9931	0.9992	0.8789	0.9694
Max slope	1.0279	1.0264	1.0767	0.9633
Min slope	0.9984	1.0157	0.7323	0.9052
Max intercept	–0.0105	–0.0001	0.1363	0.0004
Min intercept	–0.0219	–0.0067	–0.0278	0.0000
$f(1,n-2,p<0.01)$	24,161	185,432	159.7	5293.3

IN-VITRO TESTS OF LOW-FLOW DOSING SCHEDULES

Table 4 gives the measured inspired gas concentrations at the end of 1 h of low-flow administration in the *in vitro* experiments. We found the mean inspired oxygen concentration achieved by the dosing schedules to be 32.8% (SD=1.9%), a discrepancy from the target concentration whose effect would be inconsequential in clinical practice. The mean inspired halothane concentration was 1.2% (SD=0.3%), but the value seen in case 2 would clearly be of concern.

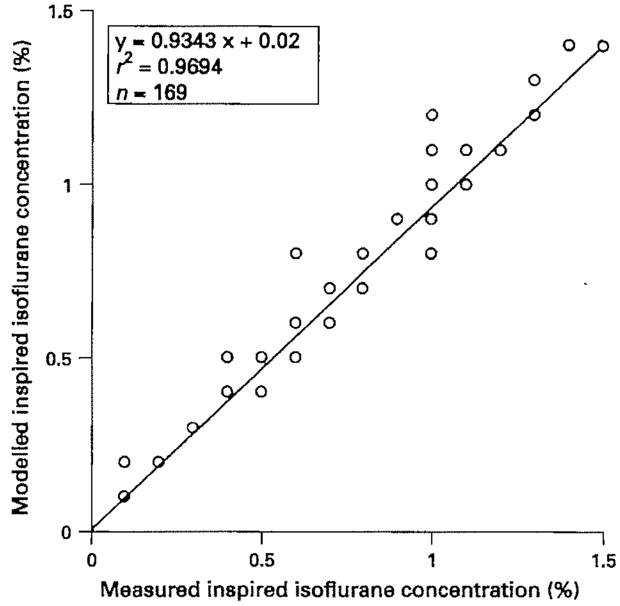


Figure 7 Modelled versus measured inspired isoflurane concentration. Note that the scales in this figure are in percent instead of fractional concentration; the y-axis intercept of the regression line is also expressed in percent. The number of data points plotted appears to be considerably less than the number used due to the manner in which the optional analog output board of the Datex AGM-103 produces its outputs. It does not provide analog sensor output voltages but instead performs digital-to-analog conversion on computed digital gas concentration values. The digital concentration values for anaesthetic agent are resolved in increments of 0.1% Thus each open circle may represent multiple data points.

Discussion

The ability of this model to reproduce the results of other mass-balance models lends credence to the correctness of this model.

We may inquire as to the origin of the small errors in the modelled inspired gas concentrations. One possible explanation is error in measuring patient gas exchanges. Measurement of exchanges during the clinical studies requires taking the difference between two nearly-equal quantities (the product of flow and concentration of fresh gases less the product of flow and concentration of the exhausted gases). The use of a common instrument to measure both concentrations mitigates the difficulties, but it was not possible to use a common flow element for both the fresh gases and exhausted gases. We do believe that the flow measurements were not grossly in error, however; measured oxygen exchange during those epochs applied to the model was –2.92 (0.55) ml min^{-1} kg^{-1} (mean (SD)), comparing well with uptake figures of 3.0 ml min^{-1} kg^{-1} [12] and 3.25 ml min^{-1} kg^{-1}.[23] The sensitivity of concentrations in the circle–absorber system to patient exchanges diminishes with fresh-gas flow; and in only one case was the mean fresh-gas flow less than 1.0 litre min^{-1}. Thus we believe error in patient gas-exchange measurement to be unlikely to explain the results. In addition, tracking error between the

Table 4 Results of testing dosing regimes derived from the mass-balance model with an gas-exchange lung simulator. Measured gas exchanges and flowmeter settings are given in ml min^{-1} at ambient conditions of 21°C and 98 8 kPa (741 mm Hg). The inspired gas concentrations are readings from the digital display of a Datex AGM-103 airway gas monitor connected to the inspired limb of the breathing circuit; multiple readings indicate that the display was seen to be dithering equally between two adjacent readings. Measured nitrous oxide concentrations appear to be high (greater than 64%) when oxygen readings are low (below 35%). As the nitrous oxide sensor and the oxygen sensor of the Datex AGM-103 are independent, the apparent negative correlation of the readings supports the belief that the oxygen and nitrous oxide concentrations are being read accurately

Case	0	1	2	3	4	5	6	7	8
$\dot{V}_{O_2}$ measured	–211	–212	–213	–218	–211	–218	–215	–214	–219
V_{N_2O} setting	0	–75	–150	0	–75	–150	0	–75	–150
V_{N_2O} measured	+19	–51	–113	+32	–50	–118	+25	–51	–122
V_{Az} setting	0	0	0	–5	–5	–5	–10	–10	–10
V_{Az} measured	–1.6	–1.8	–3.1	–4.8	–4.9	–5 3	–7.4	–7.6	–7.9
O_2 flowmeter	350	329	309	359	328	311	355	330	310
N_2O flowmeter	250	271	291	241	273	289	245	270	290
Vapouriser, %	0.96	0.87	0.97	1 47	1.38	1.31	1.89	1 81	1 74
Inspired O_2, %	31	33–34	36	32–33	30–31	34–35	31	31–32	34–35
Inspired N_2O, %	70	67	63–64	67–68	70	65–66	70	70	66
Inspired agent, %	1.4	1.4–1 5	1.7–1.8	1.1–1.2	1.1–1.2	1.1	0.9–1.0	0.9	0.8

two Datex instruments cannot entirely account for discrepancies between the model and measured results. For example, the modelled-to-measured inspired oxygen concentration differential was −1.12% (0.59)% (mean (SD)) which exceeds the measured tracking error of the two Datex instruments at oxygen concentrations of 25% (where the difference of the gas-exchange Datex reading and that of the second Datex was +0.56%) and 50% (where the instruments differed by +0.28%).

The utility of the mass-balance model assumes that rates of gas exchange are constant or quasi-constant. This assumption is not unrealistic. The pronounced non-linearity of the oxyhaemoglobin dissociation curve causes oxygen uptake to be constant for inspired oxygen partial pressures exceeding 12.0 kPa (90 mm Hg),[24] while uptakes of nitrous oxide and anaesthetic agents diminish slowly (over tens of minutes) once initial washing has taken place.[25] Constant uptakes of anaesthetic gases (including nitrous oxide) are a useful approximation for the time period from 20 min to 2 h into an anaesthetic case.[26] Figures 8 and 9 show specific exchanges (ml min^{-1} kg^{-1} per percentage inspired) of nitrous oxide and isoflurane, respectively. The nitrous oxide data of figure 8 do show a slow decline in exchange as the case proceeds. Those data points showing a positive exchange (patient producing nitrous oxide) all came from the paediatric case; it is not apparent why washout was seen in this one case. We note that figure 9 shows a fairly constant exchange of isoflurane (the data points at the upper right figure 9 were taken after administration of isoflurane was ended in the case of the 22-yr-old male). Table 5 summarizes measured specific exchanges in 15-min increments from 15 min to 3 h during maintenance of anaesthesia cases (data showing apparent washout have been excluded). We may justify exclusion of data from washout in table 5 because low-flow technique would chiefly be applied to maintenance of anaesthesia cases.

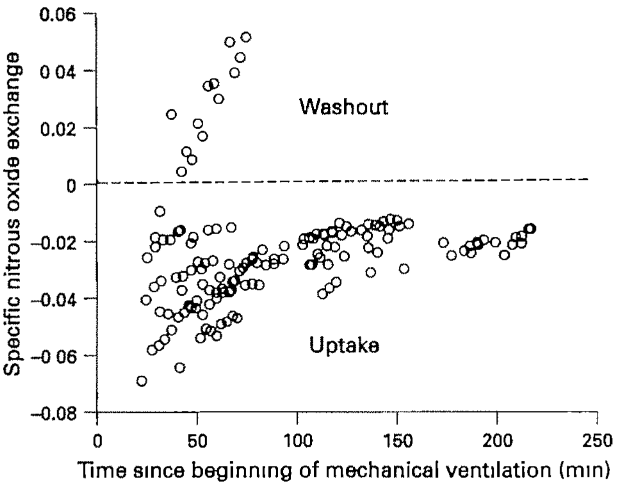


Figure 8 Specific exchanges (ml min^{-1} kg^{-1} per percent inspired) for nitrous oxide. Those points representing washout (specific exchange >0) all come from the paediatric case.

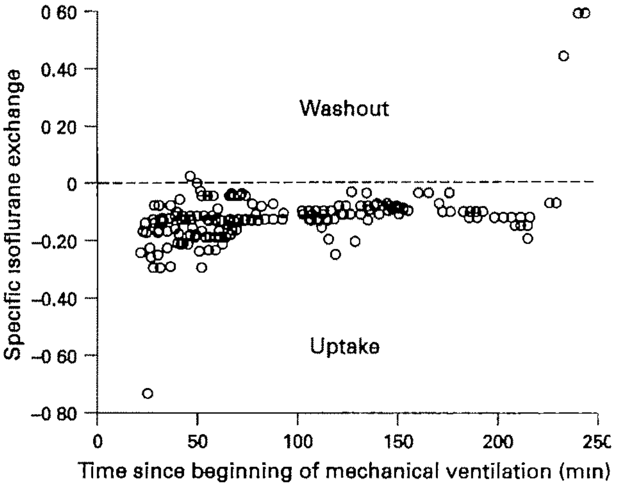


Figure 9 Specific exchanges (ml min^{-1} kg^{-1} per percent inspired) for isoflurane.

Analysis of the *in vitro* experiment is somewhat more complex. The error in inspired halothane concentration was strongly correlated to the measured halothane exchange of the lung (r=0.87), indicating that the error increased as uptake decreased. The model shows the inspired halothane concentration to have high sensitivity to halothane exchange, ranging from 0.23% $\text{ml}^{-1}\,\text{min}^{-1}$ for case 0 to 0.37% $\text{ml}^{-1}\,\text{min}^{-1}$ for case 8. The computed sensitivity for case 2 (which had the largest error in inspired halothane concentration) is 0.35% $\text{ml}^{-1}\,\text{min}^{-1}$. Thus, were the actual lung halothane uptake in case 2 to be less than the 'sealed lung' value by 2 ml min^{-1}, the inspired concentration would rise by 0.7%. We may question whether the 'sealed lung' gas exchange values remain unchanged when the lung is connected to the breathing circuit and subjected to intermittent positive-pressure ventilation; and the minimum increment of anaesthetic agent exchange in the active lung is 2 ml min^{-1}

Table 5 Measured specific exchanges (litre min^{-1} per percent of inspired concentration) of nitrous oxide and isoflurane *vs* time from surgical cases. Times are measured since the start of mechanical ventilation; *n* indicates the number of data epochs taken during a particular time interval.

Time, min	Specific nitrous oxide exchange (mean (SD))	*n* Nitrous oxide	Specific isoflurane exchange (mean (SD))	*n* Isoflurane
15–30	−0.039 (0.019)	7	−0.234 (0.178)	11
30–45	−0.037 (0.016)	17	−0.160 (0.064)	24
45–60	−0.036 (0.012)	23	−0.139 (0.076)	28
60–75	−0.036 (0.009)	17	−0.121 (0.056)	22
75–90	−0.029 (0.004)	9	−0.109 (0.026)	9
90–105	−0.023 (0.003)	4	−0.110 (0.013)	4
105–120	−0.025 (0.007)	17	−0.130 (0.040)	17
120–135	−0.018 (0.004)	8	−0.096 (0.048)	10
135–150	−0.019 (0.006)	10	−0.090 (0.017)	12
150–165	−0.019 (0.008)	4	−0.085 (0.023)	7
165–180	−0.024 (0.003)	2	−0.071 (0.034)	5

because of the resolution and quantitation of the lung gas concentration monitor. It is thus plausible that the discrepancies in inspired halothane concentration result more from the test lung apparatus rather than structural problems with the model.

It is worth noting that the model predicted in cases 1–3 that the required vapourizer settings were less than the desired inspired halothane concentration. This apparently anomalous situation develops if the ratio of uptake of halothane to fresh halothane vapour is less than the net uptake of other gases relative to their fresh gas flows. In case 2 where the computed vapourizer setting is 0.87%, for example, the combined uptakes of oxygen and nitrous oxide represent 48% of their fresh gas inputs, compared with a halothane uptake of 34% of its fresh gas input. By contrast, the net uptake of oxygen and nitrous oxide in case 6 amounts to 32% of their fresh gases while the halothane uptake is 65% of its fresh gas input; the model gave a vapourizer setting of 1.89% for this case.

The sensitivity of inspired concentrations to agent exchanges under low-flow conditions is readily apparent from these results. This may appear to be a serious drawback to the use of the model in the clinical setting where the anaesthetic uptakes of any given patient are not *a priori* knowable and may vary considerably from patient to patient.[27] The volume of the circle–absorber system, however, serves as a buffer after being primed with the desired concentrations,[18] guaranteeing that clinically-unacceptable concentrations of anaesthetic agent will not develop rapidly even if estimated anaesthetic uptake is in error.

We conclude that the three-chamber mass-balance model is a valid representation of the circle-absorber system and that it may be used to compute flowmeter and vapourizer settings for low-flow anaesthesia. The chief difficulty we foresee in its application is the wide range of patient exchanges of anaesthetic agents. We propose, however, that uptake models (for example, as described by Lerou and colleagues[28]) may be used to find nominal exchanges of anaesthetic gases for a patient of a given body mass and that these, coupled with estimated patient oxygen exchange (also based on body mass), may be used to compute an initial solution for the flowmeter and vapourizer settings. Active monitoring during the case would permit periodic correction of these estimates.

Appendix 1

DERIVATION AND MATRIX SOLUTION OF THE MODEL

Refer to figure 1. Fresh gas (whose flow is denoted by $\dot{V}_{\mathrm{F}}$) enters the system at the upper left and it is divided into two portions by the inspiratory check value. Gases entering during inspiration (represented by $\dot{V}_{\mathrm{FI}}$) are routed directly to the inspiratory path; gases entering during expiration are routed into the absorber and are designated by $\dot{V}_{\mathrm{FAb}}$. The duration of inspiration is denoted by I and that of expiration by E; we define a factor $k_{\mathrm{I}}=I/(I+E)$ to represent the ratio of the inspiratory period to the total ventilatory period. The partitioning of $\dot{V}_{\mathrm{F}}$ is thus given by $\dot{V}_{\mathrm{FI}}=k_{\mathrm{I}}\dot{V}_{\mathrm{F}}$ and $\dot{V}_{\mathrm{FAb}}=(1-k_{\mathrm{I}})\dot{V}_{\mathrm{F}}$.

The flow of gases between the absorber and the bellows reverses direction with ventilatory phase. This alternating gas flow is represented by two opposing continuous mean-valued flows; $\dot{V}_{\mathrm{AbB}}$ represents the gas leaving the absorber in the direction of the bellows, while $\dot{V}_{\mathrm{BAb}}$ denotes the gas leaving the bellows in the direction of the absorber. Flow $\dot{V}_{\mathrm{BAb}}$ will equal the ventilator's delivered minute ventilation; flow V_{AbB} is gas displaced from the absorber by fresh gas during expiration. Flow $\dot{V}'_{\mathrm{AbB}}$ represents the absorber gas reaching the bellows, while $\dot{V}'_{\mathrm{BAb}}$ designates the bellows gas reaching the absorber. Typically, $\dot{V}'_{\mathrm{AbB}}=\dot{V}_{\mathrm{AbB}}$ and $\dot{V}'_{\mathrm{BAb}}=V_{\mathrm{BAb}}$, but our model permits a net leak of gas to the atmosphere (denoted by $\dot{V}_{\mathrm{L_{BAb}}}$) between the bellows and absorber. Parameter $k_{\mathrm{L_{BAb}}}$ specifies the proportion of $\dot{V}_{\mathrm{L_{BAb}}}$ which occurs during inspiration (and is taken from $\dot{V}_{\mathrm{BAb}}$). For a pressure-driven leak (which would occur almost exclusively during inspiration), $k_{\mathrm{L_{BAb}}} \approx 1$; for a constant withdrawal of gas by a sampling device (such as a respiratory gas monitor), $k_{\mathrm{L_{BAb}}} \approx k_{\mathrm{I}}$. This apportioning is required because the composition of the gas in the bellows-to-absorber path changes with ventilatory phase (bellows gas during inspiration, absorber gas during expiration). A bellows-to-absorber leak would likely be pressure-driven because this is not a typical point for gas sampling. Carbon dioxide entering the absorber will be scrubbed with an efficiency denoted by η; a value of 1 indicates complete scrubbing, while 0 indicates no scrubbing. Scrubbing causes gas outflows from the absorber to be less than the inflows if the inflowing gases contain carbon dioxide:

$$\dot{V}_{\mathrm{AbB}}=\dot{V}_{\mathrm{FAb}}(1-\eta\ F_{\mathrm{F_{CO_2}}}) \tag{A1a}$$

$$\dot{V}_{\mathrm{AbI}}=\dot{V}_{\mathrm{BAb}}(1-\eta\ F_{\mathrm{B_{CO_2}}}) \tag{A1b}$$

where $F_{\mathrm{F_{CO_2}}}$ and $F_{\mathrm{B_{CO_2}}}$ are the fractional concentrations of carbon dioxide in the fresh gas and bellows gas, respectively, and V_{AbI} is the mean outflow from the absorber into the inspiratory path.

The total influx of gas into the inspiratory path is $\dot{V}_{\mathrm{FI}}+\dot{V}_{\mathrm{AbI}}$. We permit a leak to the atmosphere from the inspiratory path ($\dot{V}_{\mathrm{L_I}}$). The total inspiratory flow ($\dot{V}_{\mathrm{I}}$) is given by.

$$\dot{V}_{\mathrm{I}}=\dot{V}_{\mathrm{FI}}+\dot{V}_{\mathrm{AbI}}-\dot{V}_{\mathrm{L_I}} \tag{A2}$$

Another leak (V_{Law}) may occur at the patient airway connection with a proportioning parameter (k_{Law}) as, neglecting the effect of deadspace, the gas at the patient airway connection will be inspiratory gas during inspiration and alveolar gas during expiration. If V_{Law} is the sampling draw of a gas monitor, $k_{\mathrm{Law}} \approx k_{\mathrm{I}}$; if it is a pressure-driven leak, $k_{\mathrm{I}} \approx 1$. Leak $\dot{V}_{\mathrm{L_I}}$ does not have a proportioning parameter because the gas composition does not change with ventilatory phase. Compliance losses, comprised of the elastance of breathing-circuit components and gas compressibility,[29] may be lumped together with patient deadspace to form a flow (V_{D}) which shunts gas from the inspiratory path to the expiratory path.[30] Inspiratory alveolar ventilation $\dot{V}_{\mathrm{AI}}$ is given by:

$$\dot{V}_{\mathrm{AI}}=\dot{V}_{\mathrm{I}}-k_{\mathrm{Law}}\dot{V}_{\mathrm{Law}}-\dot{V}_{\mathrm{D}} \tag{A3}$$

The gas flows entering the alveolar compartment are the inspiratory inflow V_{AI} and the sum of patient alveolar gas exchanges $\dot{V}_{\mathrm{pat}}$ where $\dot{V}_{\mathrm{pat}}$ is a vector with one element for each gas (for example, $V_{\mathrm{O_2}}, V_{\mathrm{CO_2}}$). Net flows into the alveolar space from the body (for example, $V_{\mathrm{CO_2}}$) are considered positive, net flows into the body from the alveolar space (for example, $V_{\mathrm{O_2}}$) are negative. Expired alveolar ventilation $\dot{V}_{\mathrm{AE}}$ equals V_{AI} plus the sum of patient gas exchanges and the portion of $\dot{V}_{\mathrm{Law}}$ drawn from alveolar gas:

$$\dot{V}_{\mathrm{AE}}=\dot{V}_{\mathrm{AI}}+\sum\dot{V}_{\mathrm{pat}}-(1-k_{\mathrm{Law}})\dot{V}_{\mathrm{Law}} \tag{A4}$$

Net expiratory flow into the bellows is given by.

$$\dot{V}_{\mathrm{E}}=\dot{V}_{\mathrm{AE}}+\dot{V}_{\mathrm{D}}-\dot{V}_{\mathrm{L_E}} \tag{A5}$$

where $V_{\mathrm{L_E}}$ is an expiratory-path leak. Summation of flows at the bellows gives:

$$\dot{V}_{\mathrm{BS}}=\dot{V}_{\mathrm{E}}+\dot{V}_{\mathrm{AbB}}-\dot{V}_{\mathrm{BAb}} \tag{A6}$$

where V_{BS} is the flow of spilt gas into the scavenging system.

Mass balance in each chamber requires the solution of the following system of simultaneous equations:

$$\dot{V}_{\mathrm{FAb}}(E.{\star}F_{\mathrm{F}})+\dot{V}_{\mathrm{BAb}}(E.{\star}F_{\mathrm{B}})-(\dot{V}_{\mathrm{AbB}}+\dot{V}_{\mathrm{AbI}})F_{\mathrm{Ab}}=0 \tag{A7a}$$

$$\dot{V}_{\mathrm{AI}}F_{\mathrm{I}}+\dot{V}_{\mathrm{pat}}-[\dot{V}_{\mathrm{AE}}+(1-k_{\mathrm{Law}})\dot{V}_{\mathrm{Law}}]F_{\mathrm{A}}=0 \tag{A7b}$$

$$\dot{V}_{\mathrm{E}}F_{\mathrm{E}}+\dot{V}_{\mathrm{AbB}}\ F_{\mathrm{Ab}}-(\dot{V}_{\mathrm{BAb}}+\dot{V}_{\mathrm{BS}})F_{\mathrm{B}}=0 \tag{A7c}$$

where F_{F}, F_{Ab}, F_{I}, F_{A}, F_{E}, and F_{B} are vectors representing fractional gas concentrations in, respectively, the fresh-gas stream, carbon dioxide absorber, inspiratory path, alveolar space, expiratory path, and the bellows; E is a vector which accounts for the selective absorption of carbon dioxide in the absorber. The ".*" notation used in equations A7a denotes element-by-element multiplication of vectors with identical dimensions. Absorption vector E and fractional concentration vectors F_{Ab}, F_{A}, and F_{B} are expressed as:

$$E=\begin{vmatrix}(1-\eta)\\1\\1\\1\\1\end{vmatrix}\quad F_{\mathrm{Ab}}=\begin{vmatrix}F_{\mathrm{Ab_{CO_2}}}\\F_{\mathrm{Ab_{N_2}}}\\F_{\mathrm{Ab_{N_2O}}}\\F_{\mathrm{Ab_{O_2}}}\\F_{\mathrm{Ab_{Ax}}}\end{vmatrix}\quad F_{\mathrm{A}}=\begin{vmatrix}F_{\mathrm{A_{CO_2}}}\\F_{\mathrm{A_{N_2}}}\\F_{\mathrm{A_{N_2O}}}\\F_{\mathrm{A_{O_2}}}\\F_{\mathrm{A_{Ax}}}\end{vmatrix}\quad F_{\mathrm{B}}=\begin{vmatrix}F_{\mathrm{B_{CO_2}}}\\F_{\mathrm{B_{N_2}}}\\F_{\mathrm{B_{N_2O}}}\\F_{\mathrm{B_{O_2}}}\\F_{\mathrm{B_{Ax}}}\end{vmatrix}\tag{A8}$$

where the subscript 'Ax' represents anaesthetic agent vapour. Vectors F_{F} and $\dot{V}_{\mathrm{pat}}$ have similar structures:

$$F_{\mathrm{F}}=\begin{vmatrix}F_{\mathrm{F_{CO_2}}}\\F_{\mathrm{F_{N_2}}}\\F_{\mathrm{F_{N_2O}}}\\F_{\mathrm{F_{O_2}}}\\F_{\mathrm{F_{Ax}}}\end{vmatrix}\quad \dot{V}_{\mathrm{pat}}=\begin{vmatrix}\dot{V}_{\mathrm{CO_2}}\\\dot{V}_{\mathrm{N_2}}\\\dot{V}_{\mathrm{N_2O}}\\\dot{V}_{\mathrm{O_2}}\\\dot{V}_{\mathrm{Ax}}\end{vmatrix}$$

The inspiratory-path gas concentration vector F_{I} may be expressed as a weighted sum of the absorber concentration vector F_{Ab} and the fresh gas concentration vector F_{F}:

$$F_{\mathrm{I}}=\frac{\dot{V}_{\mathrm{FI}}F_{\mathrm{F}}+\dot{V}_{\mathrm{AbI}}F_{\mathrm{Ab}}}{F_{\mathrm{FI}}+\dot{V}_{\mathrm{AbI}}}\tag{A10}$$

Expiratory-path gas concentration vector F_{E} is a weighted combination of the alveolar gas concentration vector F_{A} and inspiratory-path gas concentration vector F_{I}:

(A9)

$$F_{\mathrm{E}}=\frac{\dot{V}_{\mathrm{AE}}F_{\mathrm{A}}+\dot{V}_{\mathrm{D}}F_{\mathrm{I}}}{\dot{V}_{\mathrm{AE}}+\dot{V}_{\mathrm{D}}}\tag{A11}$$

By combining Eqs. (A10) and (A11), we may express F_{E} in terms of F_{A}, F_{F} and F_{Ab}:

$$F_{\mathrm{E}}=\frac{\dot{V}_{\mathrm{AE}}(\dot{V}_{\mathrm{FI}}+\dot{V}_{\mathrm{AbI}})F_{\mathrm{A}}+\dot{V}_{\mathrm{D}}(\dot{V}_{\mathrm{FI}}F_{\mathrm{F}}+\dot{V}_{\mathrm{AbI}}F_{\mathrm{Ab}})}{(\dot{V}_{\mathrm{FI}}+\dot{V}_{\mathrm{AbI}})(\dot{V}_{\mathrm{AE}}+\dot{V}_{\mathrm{D}})}\tag{A12}$$

We thus see from equations (A10) and (A12) that the inspiratory concentrations F_{I} and expiratory concentrations F_{E} may be computed from the various gas flows, fresh-gas concentration F_{F}, and chamber-gas concentrations F_{Ab}, F_{A}, and F_{B}. The complete system of mass–balance equations may be written in a compact matrix form:

$$A\begin{vmatrix}F_{\mathrm{Ab}}\\F_{\mathrm{A}}\\F_{\mathrm{B}}\end{vmatrix}+B\begin{bmatrix}F_{\mathrm{F}}\\\dot{V}_{\mathrm{pat}}\end{bmatrix}=[0]\tag{A13}$$

where A and B are matrices described below.

The mass flows among the chambers are represented by the matrix product of A and F_{Ab}, F_{A}, and F_{B}. All elements of A have dimensions of flow; A is given by:

$$A=\begin{vmatrix}
A_1&0&0&0&0&0&0&0&0&0&\dot{V}_{\mathrm{BAb}(1-\eta)}&0&0&0&0\\
0&A_1&0&0&0&0&0&0&0&0&0&\dot{V}_{\mathrm{BAb}}&0&0&0\\
0&0&A_1&0&0&0&0&0&0&0&0&0&\dot{V}_{\mathrm{BAb}}&0&0\\
0&0&0&A_1&0&0&0&0&0&0&0&0&0&\dot{V}_{\mathrm{BAb}}&0\\
0&0&0&0&A_1&0&0&0&0&0&0&0&0&0&V_{\mathrm{BAb}}\\
A_2&0&0&0&0&A_4&0&0&0&0&0&0&0&0&0\\
0&A_2&0&0&0&0&A_4&0&0&0&0&0&0&0&0\\
0&0&A_2&0&0&0&0&A_4&0&0&0&0&0&0&0\\
0&0&0&A_2&0&0&0&0&A_4&0&0&0&0&0&0\\
0&0&0&0&A_2&0&0&0&0&A_4&0&0&0&0&0\\
A_3&0&0&0&0&A_5&0&0&0&0&A_6&0&0&0&0\\
0&A_3&0&0&0&0&A_5&0&0&0&0&A_6&0&0&0\\
0&0&A_3&0&0&0&0&A_5&0&0&0&0&A_6&0&0\\
0&0&0&A_3&0&0&0&0&A_5&0&0&0&0&A_6&0\\
0&0&0&0&A_3&0&0&0&0&A_5&0&0&0&0&A_6
\end{vmatrix}\tag{A14}$$

where:

$$A_1=-(\dot{V}_{\mathrm{AbI}}+\dot{V}_{\mathrm{AbB}})\tag{A15a}$$

$$A_2=\frac{\dot{V}_{\mathrm{AbI}}(\dot{V}_{\mathrm{AbI}}+\dot{V}_{\mathrm{FI}}-\dot{V}_{\mathrm{LI}}-k_{\mathrm{Law}}\dot{V}_{\mathrm{Law}}-\dot{V}_{\mathrm{D}})}{\dot{V}_{\mathrm{AbI}}+\dot{V}_{\mathrm{FI}}}\tag{A15b}$$

$$A_3=\dot{V}_{\mathrm{AbB}}+\frac{\dot{V}_{\mathrm{D}}\dot{V}_{\mathrm{AbI}}(\dot{V}_{\mathrm{AE}}+\dot{V}_{\mathrm{D}}-\dot{V}_{\mathrm{L_E}})}{(\dot{V}_{\mathrm{AE}}+\dot{V}_{\mathrm{D}})(\dot{V}_{\mathrm{FI}}+\dot{V}_{\mathrm{AbI}})}\tag{A15c}$$

$$A_4=-[\dot{V}_{\mathrm{AE}}+(1-k_{\mathrm{Law}})\dot{V}_{\mathrm{Law}}]\tag{A15d}$$

$$A_5=\frac{\dot{V}_{\mathrm{AE}}(\dot{V}_{\mathrm{AE}}+\dot{V}_{\mathrm{D}}-\dot{V}_{\mathrm{L_E}})}{\dot{V}_{\mathrm{AE}}+\dot{V}_{\mathrm{D}}}\tag{A15e}$$

$$A_6=-(\dot{V}_{\mathrm{BAb}}+\dot{V}_{\mathrm{BS}})\tag{A15f}$$

The matrix product of B with the fresh-gas concentrations F_{F} and patient exchanges $\dot{V}_{\mathrm{pat}}$ represents the mass flows entering and leaving the system. The B matrix is given by:

$$B=\begin{vmatrix}
\dot{V}_{\mathrm{FAb}}(1-\eta)&0&0&0&0&0&0&0&0&0\\
0&\dot{V}_{\mathrm{FAb}}&0&0&0&0&0&0&0&0\\
0&0&\dot{V}_{\mathrm{FAb}}&0&0&0&0&0&0&0\\
0&0&0&V_{\mathrm{FAb}}&0&0&0&0&0&0\\
0&0&0&0&V_{\mathrm{FAb}}&0&0&0&0&0\\
B_1&0&0&0&0&1&0&0&0&0\\
0&B_1&0&0&0&0&1&0&0&0\\
0&0&B_1&0&0&0&0&1&0&0\\
0&0&0&B_1&0&0&0&0&1&0\\
0&0&0&0&B_1&0&0&0&0&1\\
B_2&0&0&0&0&0&0&0&0&0\\
0&B_2&0&0&0&0&0&0&0&0\\
0&0&B_2&0&0&0&0&0&0&0\\
0&0&0&B_2&0&0&0&0&0&0\\
0&0&0&0&B_2&0&0&0&0&0
\end{vmatrix}$$

where:

$$B_1=\frac{\dot{V}_{\mathrm{FI}}(\dot{V}_{\mathrm{AbI}}+\dot{V}_{\mathrm{FI}}-\dot{V}_{\mathrm{L_I}}-k_{\mathrm{Law}}\dot{V}_{\mathrm{Law}}-\dot{V}_{\mathrm{D}})}{\dot{V}_{\mathrm{FI}}+\dot{V}_{\mathrm{AbI}}}\tag{A17a}$$

$$B_2=\frac{\dot{V}_{\mathrm{D}}\dot{V}_{\mathrm{FI}}(\dot{V}_{\mathrm{AE}}+\dot{V}_{\mathrm{D}}-\dot{V}_{\mathrm{L_E}})}{(\dot{V}_{\mathrm{FI}}+\dot{V}_{\mathrm{AbI}})(\dot{V}_{\mathrm{AE}}+\dot{V}_{\mathrm{D}})}\tag{A17b}$$

(A16)

The null vector [0] is of size 15×1.

MATRIX SOLUTION OF THE MASS-BALANCE EQUATIONS

The matrix equations of equation (A13) are non-linear because elements of both the A and B matrices depend indirectly (through $\dot{V}_{\mathrm{AbI}}$) upon the bellows concentration of carbon dioxide ($F_{\mathrm{B_{CO_2}}}$). Solution to this system uses the iterative Newton–Raphson algorithm for matrices.[31]

PROGRAMMING LANGUAGE AND COMPUTER PLATFORMS

The mass-balance model is written in MATLAB (The Math Works, Natick, MA, USA) and runs under MATLAB for DOS or Windows on PC-compatible machines; it is portable to UNIX-based installations of MATLAB as well. Model execution is rapid; experience shows that it typically converges in four iterations.

Appendix 2

COMPUTATION OF LOW-FLOW DOSING SCHEDULES

Use of the model to compute dosing schedules requires knowledge of ventilatory parameters (*I:E* ratio, minute ventilation, and fresh-gas flows) and an *a priori* estimate of patient gas exchanges. A published[28,32] non linear formula for oxygen consumption is

$V_{O_2}=0.01M^{0.75}$ where $\dot{V}_{O_2}$ is in litres^{-1} and M is the body mass in kg A linear relationship of 3 ml min^{-1} kg^{-1} is also found in the literature.[12] These two formulae do not differ greatly for adult patients; the non-linear relationship gives an oxygen consumption of 242 ml min^{-1} for a 70 kg adult, whilst the linear relationship gives 210 ml min^{-1}.(Negative signs must be used with these figures to conform to the model's convention that patient gas uptakes are negative.) Estimates of anaesthetic exchanges may be found in numerous references, for example, Lin.[25]

An estimate of shunt $\dot{V}_D$ may be made by:

$$\dot{V}_D=f\cdot(\dot{V}_D+C_cP_{\text{aw,peak}}) \tag{A18}$$

where V_D is the patient deadspace, f is the ventilatory frequency, C_c is the compliance of the breathing circuit, and $P_{\text{aw,peak}}$ is the peak airway pressure during inspiration. We may relate patient deadspace to body mass at 2.2 ml kg^{-1} in normal subjects and approximately half that in intubated subjects[19 20]; experimental compliance figures are found in.[29] Maximal airway pressure is measured in the clinical setting. The estimate of V_D derived in this manner is apt to be an educated guess, but inspired and expired concentrations will be unaffected even if it is in error, as an error in V_D will principally affect the alveolar concentrations. We presume that other ventilatory parameters are known (rate, minute ventilation, ratio of I to E).

Let F_I^* represent the vector of target inspiratory concentrations. We assume initial guesses for the flows of each fresh gas and for the vapourizer setting. The model is then used to calculate inspired concentrations and the sum-squared error ε of the calculated and target inspired concentrations is computed:

$$\varepsilon=\sum_{k=1}^{n}(F_{Ik}-F_{Ik}^{\star})^2 \tag{A19}$$

where n is the number of gases, F_{Ik} is the computed inspired fractional concentration of the k^{th} gas and F_{Ik}^* is the target inspired concentration of the k^{th} gas. If ε is sufficiently small (typically <0.0001), the process terminates. Otherwise, the partial derivatives of ε with respect to the flow of oxygen and the vapourizer setting are computed. The next estimate of the oxygen flowmeter setting is:

$$\dot{V}_{F_{O_2}}(n+1)=\dot{V}_{F_{O_2}}(n)-\alpha\frac{\partial\varepsilon}{\partial\dot{V}_{F_{O_2}}} \tag{A20}$$

where α is a parameter determined empirically as a compromise between rapidity and stability of convergence. Similarly, the next vapourizer setting is computed by:

$$F_{F_{Ax}}(n+1)=F_{F_{Ax}}(n)-\beta\frac{\partial\varepsilon}{\partial F_{F_{Ax}}} \tag{A21}$$

where β is also an empirically-chosen parameter. The change in the flow of the balance gas (nitrous oxide or nitrogen in cases in which air is administered) is equal to and opposite the change in oxygen flow from equation (A20). In cases involving air, the fresh-gas oxygen flow computed by equation (A20) is the sum of the oxygen flowmeter setting and 0.21 times the air flowmeter setting The process is repeated until ε is sufficiently small.

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Accuracy and precision of "deep sternal" and tracheal temperatures at high- and low-fresh-gas flows

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Summary

The accuracy of tracheal temperature as a measure of core temperature is relatively poor during high-flow ventilation (6 litre min^{-1} fresh-gas flow). It is unknown if accuracy improves when lower fresh-gas flow rates are used. We tested the hypothesis that tracheal temperature accuracy would improve with low-flow ventilation (1 litre min^{-1}). We studied 20 ASA Physical Status I and II patients undergoing general anaesthesia for lower abdominal surgery. Deep body temperatures were measured at the middle of the sternum using a Coretemp "deep-tissue" thermometer. Tracheal temperatures were monitored from thermistors incorporated into the tracheal tube cuffs. Oesophageal temperatures were measured from thermocouples incorporated into stethoscopes positioned at the point of maximal heart sounds. Sternal temperature correlated reasonably well with distal oesophageal temperatures, both being within the 0.5 °C cut-off for accuracy and precision. Tracheal temperatures were lower than oesophageal temperatures during both high- and low-flow ventilation. Tracheal temperatures were 0.7 °C less during high-flow ventilation and 0.9 °C less during low-flow ventilation. The precision in both cases was adequate. We conclude that tracheal temperatures were insufficiently accurate for routine clinical use, even when fresh- gas flow was restricted to 1 litre min^{-1}. In contrast, the deep temperatures were sufficiently accurate and precise for routine clinical use. (*Br. J. Anaesth.* 1998, **81**: 171–175)

Keywords. Equipment, deep-tissue thermometer; measurement, fresh-gas flow; temperature, core; temperature, deep; temperature, measurement; temperature, tracheal

Perioperative thermal perturbations are common.[1] Anaesthesia inhibits normal temperature control and this and exposure to a cold environment causes hypothermia.[2] The initial decrease in core temperature, caused by a core-to-peripheral redistribution of body heat,[3] is followed by net loss of heat to the environment.[4] Hypothermia may be induced therapeutically because only 1–3 °C reduction in core temperature provides substantial protection against cerebral ischaemia.[5 6] Conversely, mild hypothermia is associated with adverse outcomes including morbid cardiac events,[7] coagulopathy,[8] prolonged post-anaesthetic recovery,[9] prolonged hospitalization and an increase in the incidence of surgical wound infection.[10] Methods are now available to induce[11] or prevent[12] intraoperative hypothermia. Increased perioperative temperatures are also common.[13–15]

Continuous core temperature monitoring is now standard practice during general anaesthesia. The tympanic membrane, distal oesophagus, pulmonary artery, and nasopharynx are generally considered reliable.[16]

Tracheal temperatures have been proposed as a convenient alternative.[17 18] A critical aspect of this technique is positioning the temperature sensor on the patient side of the tracheal tube cuff, thereby limiting direct cooling by ventilatory gases. Despite this precaution, the accuracy of this site is relatively poor during high-flow ventilation (6 litre min^{-1} fresh-gas flow).[19] The accuracy of tracheal temperatures when lower fresh-gas flow rates are used is unknown. We tested the hypothesis that tracheal temperature accuracy would improve with low-flow ventilation and then be sufficiently accurate for routine use.

"Deep" sternal temperature has also proven sufficiently accurate for clinical use[19]; this method depends on a technique developed by Fox[20] and subsequently refined by Togawa.[21] As Fox introduced originally "deep" sternal temperature as a core temperature not under general anaesthesia,[20] we also tested the hypothesis that "deep" sternal temperature would improve its accuracy under low flow in a breathing system compared with high flow, because the lung and respiratory tracts connected to a breathing circuit are located underneath the sternum.

Methods

With approval of the Ethics Committee of the Yamanashi Medical University Hospital, we studied 20 ASA Physical Status I and II patients undergoing lower abdominal gynaecological surgery expected to last at least 2 h. Medication before anaesthesia consisted of atropine 0.5 mg and midazolam 1.5–2.0 mg

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administered i.m. General anaesthesia was induced with propofol 2 mg kg^{-1}; vecuronium bromide was then given to facilitate tracheal intubation. A Trachelon tracheal tube (Terumo Corp., Tokyo, Japan) was inserted and positioned using standard clinical criteria (with the cuff passed 1 cm beyond the vocal cords under direct visualization). The tracheal cuff was inflated sufficiently to prevent gas leak at a sustained pulmonary pressure of 30 cm H_2O.

General anaesthesia was maintained with isoflurane (1.0–3.0%) in nitrous oxide. The lungs of 10 patients who were randomly assigned, were mechanically ventilated using a partial re-breathing system (Modulus CD, Ohmeda, Liberty Corner, NJ, USA), at a fresh-gas flow rate of 6 litre min^{-1}; the lungs of 10 others were ventilated with a fresh-gas flow rate of 1 litre min^{-1}, to maintain end-tidal $P\mathrm{c}_{\mathrm{O}_2}$ near 35 mm Hg. Additional vecuronium was administered, as needed, to maintain 1–2 twitches in response to supramaximal electrical stimulation of the ulnar nerve at the wrist. Respiratory gases were not warmed or humidified. A full-length circulating-water mattress heated to 38 °C was positioned under each patient. I.v. fluids were warmed to 37 °C and ambient room temperature was maintained near 23 °C. A single layer of standard surgical draping covered each patient.

Deep body temperature was measured at the middle of the sternum using a Coretemp "deep-tissue" thermometer (Terumo Corp., Tokyo, Japan). The sensor element, 2.5 cm in diameter, was fixed securely with tape at the time of anaesthetic induction. Tracheal temperature was monitored from thermistors incorporated into the tracheal tube cuff (Terumo Corp.). Distal oesophageal temperature was measured from a thermocouple incorporated into the oesophageal stethoscope (Mallinckrodt Anaesthesiology Products, Inc., St. Louis, MO, USA). The stethoscope was positioned at the point of maximal heart sounds. Temperatures were recorded at 15-min intervals, starting 15 min after induction of anaesthesia.

Distal oesophageal temperature was considered the reference value. Temperatures at the other two sites were compared with oesophageal temperature using regression and Bland and Altman analyses.[22] We decided *a priori* that an accuracy (mean difference between reference and test temperatures) and precision (standard deviation of the difference) of 0.5 °C was clinically adequate. The limit of 0.5 °C was chosen because this variation is typical for other commonly used temperature measuring sites such as the axilla and mouth,[23 24] and because we have used this value previously . Results are expressed as means (SD and range).

Results

Characteristics of the patients whose lungs were ventilated with high- and low-fresh gas flows were comparable (table 1). Oesophageal temperatures ranged from 34.5 to 37.3 °C.

Sternal temperature correlated reasonably well with distal oesophageal temperatures, both being within the 0.5 °C cut-off for accuracy and precision. Fresh-gas flow did not much influence the accuracy of either site. The correlation between tracheal and oesophageal temperatures was relatively poor during high-flow ventilation, and no better when fresh-gas flow was restricted to 1 litre min^{-1} (table 2, figs. 1 and 2).

Discussion

Tracheal temperatures were not especially accurate, having a mean offset (reference minus tracheal temperature) of 0.7 °C during high-flow ventilation. This result is consistent with previous observations.[19] However, the offset remained high (0.9 °C) during low-flow ventilation. We thus failed to confirm our hypothesis that a fresh-gas flow of only 1 litre min^{-1} would improve the accuracy of this measurement site. Interestingly, the precision of tracheal temperature measurements was acceptable with either high- or low-flow ventilation. These data suggest that tracheal temperature measurements are not especially variable, but that they consistently underestimate core temperature by 0.7–0.9 °C. The site might thus yet prove useful if an appropriate compensation is built into the tracheal temperature monitoring system.[25]

A fresh-gas flow of only 1 litre min^{-1} significantly increases airway temperature.[26] However, a simple heat- and moisture-exchanger increases gas temperature considerably more.[27] Active airway heating and humidification, naturally, increases ventilatory gas temperature still more.[28] It seems likely that tracheal temperatures will better approximate core temperature in patients given passive or active gas conditioning. However, this potential accuracy improvement is itself problematic because different offset compensations would be required depending on the type of airway heating used.

Although the same breathing system was used with soda-lime for both low- and high-flow groups, the physical conditions such as temperature and relative humidity of both high- and low-flow inspired gases would differ. With a low-flow rate, oesophageal temperatures should be higher than with a high-flow rate because heat loss from the gas should be less. This could explain why at "low flow" the differences in both cases were greater than at high flow in figs 2 (A) and 2

Table 1 Patient characteristics. Values are expressed as mean (SD), [range]. BSA: body surface area, LBM: lean body mass

	Age (yr)	Height (cm)	Weight (kg)	BSA (m^2)	LBM (kg)
High flow	56 (12) [41–73]	156 (7) [147–168]	55 (7) [45–65]	1.6 (0 1) [1.4–1.8]	44 (5) [38–52]
Low flow	49 (13) [27–67]	156 (7) [147–166]	52 (7) [39–62]	1.5 (0.1) [1.3–1.7]	43 (5) [34–49]

Table 2 Distal oesophageal temperature compared with "deep sternal" and tracheal temperatures during high- and low-flow anaesthesia. See fig. 1 for the regression lines and fig. 2 for the mean (SD) of the differences as outlined in the Bland-Altman plots

	$T_{sternum}$		$T_{trachea}$	
Gas flow	High	Low	High	Low
r^2	0.72	0.85	0.58	0.68
Slope	0.93	0.97	0.92	0.84
Mean (°C)	0.0	0.5	0.7	0.9
SD (°C)	0.3	0.2	0.3	0.4

(B). In contrast, "deep" sternal temperature correlates well with oesophageal temperature even when the respiratory tract was ventilated with high-gas flow.

Deep temperature measurements are based on heat flux.[20 21] The system, in essence, consists of a heater positioned over a thermal flux transducer. The heater is then servo-controlled to null heat flux. Without a flow of heat across the transducer, the second law of thermodynamics specifies that temperatures must be equal on each side of the transducer (that is, heater and skin). So long as one is willing to assume an infinitely wide transducer/heater disk, the same logic applies to the tissue planes under the monitor; each must also be at the same temperature otherwise heat would accumulate in one region, again violating the second law. Of course the disk is not infinitely wide and convective flow of heat perturbs the theoretical thermal steady state. Nevertheless, deep temperature monitors usually measure tissue temperature adequately to a depth of roughly 2 cm.[29] Over the sternum, this depth apparently is sufficient to register core temperature. Deep temperatures proved sufficiently accurate for routine clinical use, having an accuracy and precision within 0.5 °C under both study conditions. This result is consistent with previous observations.[19] Although Fox published his first article regarding "deep" temperature systems in 1970, only Japanese anaesthetists have tested its clinical usefulness. Because the monitoring system using his theory is only commercially available in Japan, we intend to investigate its accuracy under various clinical situations.

We used oesophageal temperature as a reference temperature. The temperature probe was incorporated into an oesophageal stethoscope. We checked the accuracy of the temperature probe location using auscultation of breath and heart sounds through the oesophageal stethoscope.[30]

Despite a warming mattress, warmed i.v. fluids and warm ambient temperature, the initial redistribution of the heat inside the body caused a wide range of variation in core temperature, between 34.5 and 37.3 °C, so we had a wide range of core temperature for this study.

An accuracy of 0.5 °C among the main reference and tracheal or "deep" temperatures was chosen, from previous papers and our experience.[19] The number of patients needed for the study was determined by power analysis using this limit of this accuracy.

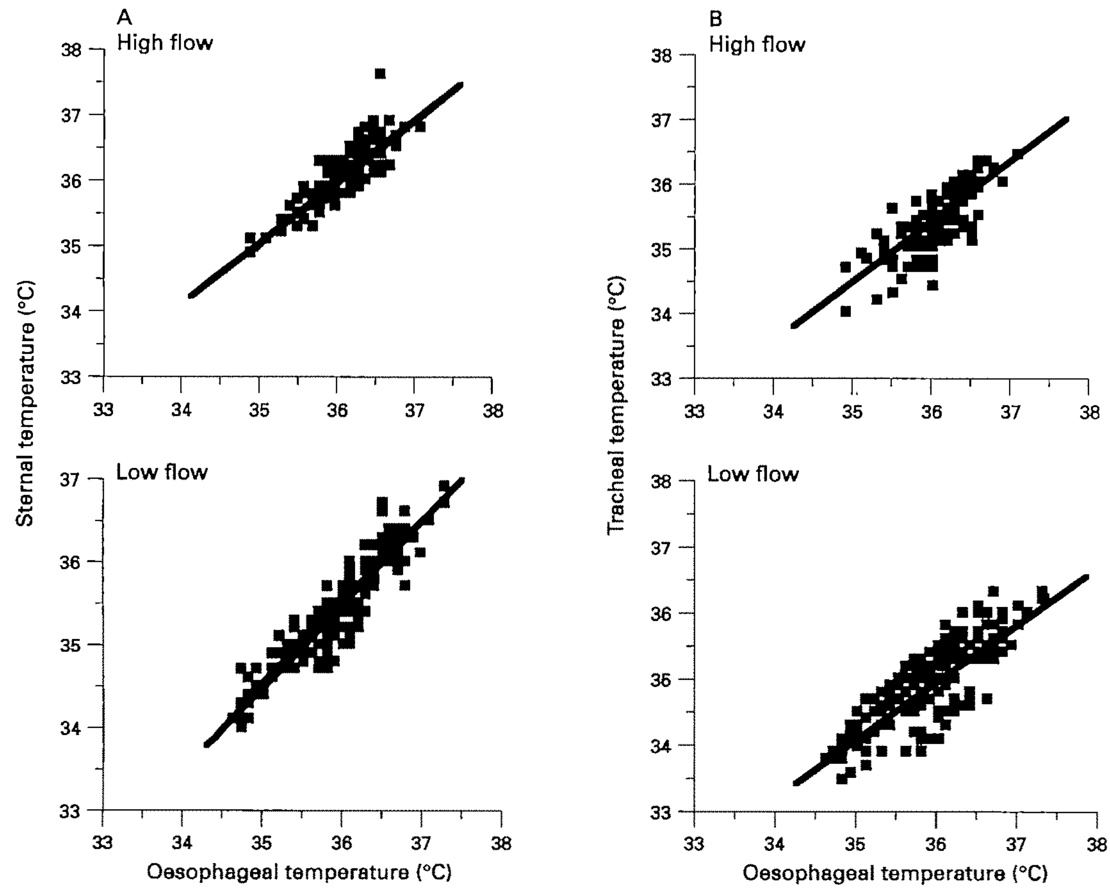

Figure 1 Regression comparison of distal oesophageal temperature with "deep sternal" (A) and tracheal (B) temperatures during high- (upper panel) and low-(lower panel) fresh-gas flows See table 2 for regression slopes and coefficients.

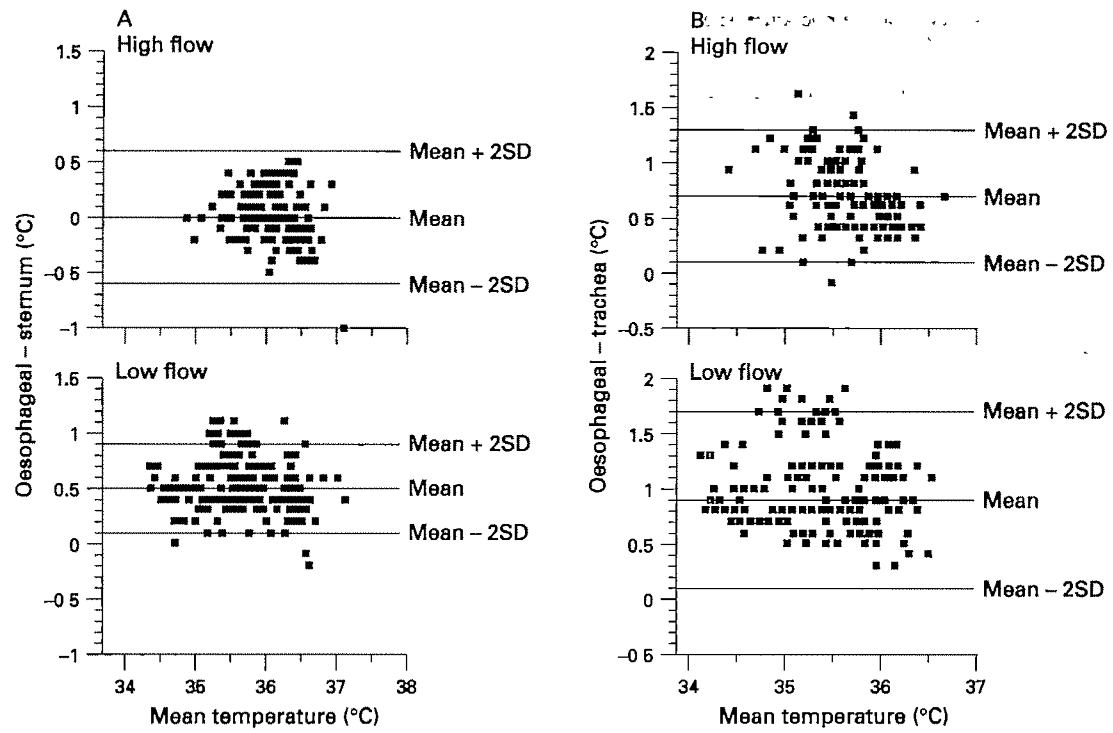

Figure 2 Bland and Altman comparison of distal oesophageal temperature with "deep sternal" (A) and tracheal (B) temperatures during high- (upper panel) and low- (lower panel) fresh-gas flows. The vertical axis is the difference between oesophageal and the test site. Mean temperature on the horizontal axis refers to the average between oesophageal and test temperatures at each measurement time. See table 2 for mean (SD) offsets

In summary, we compared distal oesophageal temperature with "deep sternal" and tracheal temperatures in 20 patients undergoing general anaesthesia with high- or low-flow ventilation for gynaecological surgery. As in previous studies, deep temperatures were sufficiently accurate and precise for routine clinical use. Tracheal temperatures, in contrast, were insufficiently accurate for routine clinical use, even when fresh-gas flow was restricted to 1 litre min^{-1}.

Acknowledgements

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Effects of a low concentration of isoflurane on contrast sensitivity in volunteers†

S. R. J. TAYLOR, O. A. KHAN, M. L. SWART, G. G. LOCKWOOD AND J. G. JONES

Summary

The effects of 0.15% quasi steady-state end-tidal isoflurane on the contrast sensitivity of five healthy volunteers were investigated by measuring their performance in computer generated letter discrimination tasks. A series of letters were displayed on a computer screen so that the luminance of the letter differed from that of the background. Two protocols were used: in the static protocol, the letter remained displayed on the screen until the subject responded, whereas in the dynamic protocol, the letter was displayed for $^1/_{72}$ s only. Isoflurane significantly decreased contrast sensitivity in both protocols in all subjects. (*Br. J. Anaesth.* 1998; **81**: 176–179)

Keywords. anaesthetics volatile, isoflurane; brain, monitoring, contrast sensitivity

Many different measures have been used in an attempt to find a sensitive, specific and repeatable measure of impairment of neuropsychological function in the recovery phase after general anaesthesia. The oculomotor system is a popular choice because this system can be treated as a "black box" producing highly repeatable, stereotypical movements. It has been shown that inhalation of isoflurane depresses peak saccadic velocity (PSV) and increases saccadic error.[1 2] It was postulated that a task involving a higher level of cognitive processing might be more sensitive to the effects of low-dose anaesthesia seen in the recovery period after general anaesthesia. To investigate this, contrast sensitivity was measured in the presence and absence of isoflurane administration by measuring performance in letter discrimination tasks.

Methods

Five healthy anaesthetists were studied. The study was approved by the Hospital Ethics Committee and informed consent was obtained from each subject. The study consisted of a 1-h experimental session; in the first half the subjects breathed oxygen, and in the second half isoflurane in oxygen, titrated to an end-tidal concentration of 0.15%. Practice sessions breathing air were conducted before the study commenced to minimize any learning effect.

CONTRAST SENSITIVITY

Contrast sensitivity can be defined as the ability to see an object against a background. If a subject is asked to identify an object at a different luminance from that of a background, the greater the luminance difference, the easier it is for the subject to correctly identify the object. Contrast is a measure of the difference in luminances, and is defined as

$$\frac{I_{\text{object}} - I_{\text{background}}}{I_{\text{background}}}$$

where I represents luminance. If the test is repeated a number of times, the probability of correctly identifying the object can be plotted against the contrast, to give a "contrast sensitivity function", which has the form of a sigmoid curve, the standard psychophysical function.

In this study, letters were displayed on a computer screen at varying luminances relative to background. The subject was informed that the letter displayed was one of 10 pre-selected letters and was asked to guess what it was (fig. 1). The advantages of this procedure are that many repeats are possible, enabling the probability of correctly identifying the letter to be estimated.

BREATHING SYSTEM

Each subject sat in a comfortable chair in front of the computer screen. They breathed room air for training runs and for experimental runs either oxygen or isoflurane in oxygen delivered from a standard anaesthetic machine via a Lack circuit attached to a physiological mouthpiece. Subjects wore a nose-clip and the end-tidal anaesthetic concentration was measured with a Datex Capnomac Ultima. The instrument was switched on for 1 h before use. The instrument was zeroed and the calibrating gas was introduced to give a 0–3% span on the isoflurane channel using Quick Cal calibration gas. Repeat zero and span checks were made throughout the study. Further analysis was made of the instrument accuracy when reading in the 0.06–0.79% range. Samples from the anaesthetic machine fitted with an isoflurane vapourizer and running as oxygen were analysed simultaneously by the Datex Ultima and a Gas

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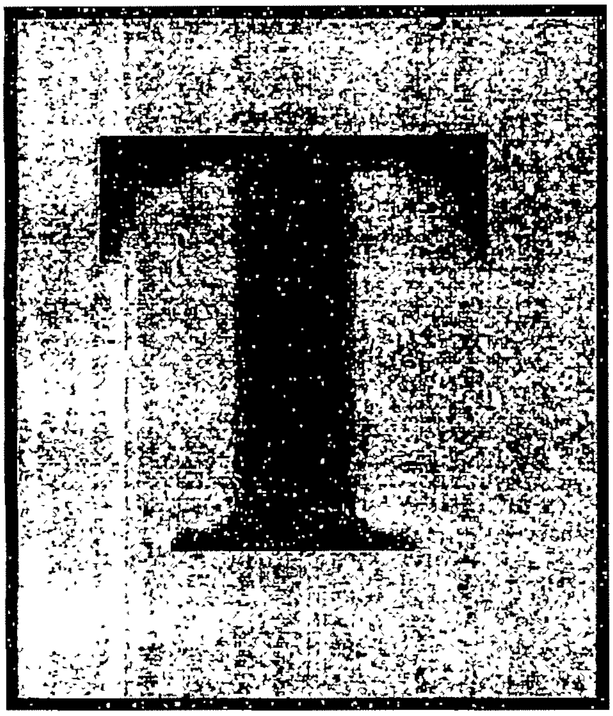

Figure 1 Screen display. A representation of the screen as displayed to the subject Contrast is defined as: $\frac{I_1-I_2}{I_1}$.

Chromatograph (GC). The GC was calibrated by six gravimetrically prepared primary standards spanning the range 0.06–0.79%. We found that an end-tidal reading of 0.1% on the Ultima was in fact a real concentration of 0.15%. In each case subjects breathed isoflurane until a real constant value of 0.15% end-tidal concentration was achieved. In each case during experimental runs subjects breathed either oxygen or isoflurane in oxygen. It was not possible to blind the subjects to the nature of the respired gas because they could taste the anaesthetic. A stable end-tidal isoflurane concentration reading was achieved for 20 min before the psychological task.

EXPERIMENTAL DESIGN

Sloan letters[3] of height and width 75 mm were displayed in a pseudo-random sequence on a black and white SVGA monitor after audible cues. The Sloan letters are a set of 10 letters (C, D, H, K, N, O, R, S, U, V) designed to be equally visible. The letters displayed were selected from four sets of 10 letters without replacement, and were presented at a luminance differing from that of the background by an amount independently selected from a series of pre-programmed values.

The pre-programmed contrast values were chosen to cover the range of the psychophysical function, so that the subject was always capable of seeing a reasonable proportion of the letter trials fairly easily to maintain subject motivation.

The subject sat approximately 1 m from the screen (note that the exact distance is unimportant[4]), and indicated on the computer keyboard what he thought the identity of the presented letter was. The subject was instructed to guess if he did not know the identity of the letter. Any input that was not one of the 10 Sloan letters was rejected, an audible warning signal was given, and the program waited for a valid input. Such errors were assumed to be the result of typing mistakes, as all 10 Sloan letters were permanently displayed on the screen. There was no time limit on the subject's response.

Each series of observations was composed of four "runs" of 50 "trials", that is, letter presentations, comprising a total of 200 observations, which took approximately 15 min. The letter presented, the subject's response and the accuracy or otherwise of this response were recorded on the computer's hard disk.

Two separate presentation protocols were performed. In the first test, the letter was presented at a luminance brighter than that of the background, and remained at this luminance until the subject made a response. This was called the "static" protocol. The second test, the "dynamic" protocol, involved the letter being flashed onto the screen for a period of 1 frame ($^1/_{72}$ s) before disappearing.

HARDWARE

The computer used was a Viglen 486 DX 33 MHz personal computer connected to a SVGA monitor. The 9-pin video card output was modified by feeding the red and blue register outputs into the green output after attenuation by a potential divider circuit to give a black and white output with finer luminance control than usual.

CALIBRATION

The screen was calibrated using a digital photometer. At the beginning of every experiment, the monitor was allowed to warm up for 1 h, in order to eliminate any heat-dependent variations in luminance. The output 0,0,0 (red register, green register, blue register) was then adjusted to a reading on 0.0±0.1 cd m^{-2} and the output 0,63,0 was adjusted to 100.0±0.1 cd m^{-2}, using the monitor's contrast control.

The photometer was also used to calibrate the output of the potential divider circuits.

SOFTWARE

A "C" program was written to present the letters and record the results. The program drew the letter and the background at the same luminance at the beginning of each trial. Background and letter luminances were then altered independently. The beginning of a new frame was awaited before any luminance changes were made, in order to avoid the luminance changing over two frames.

ANALYSIS OF RESULTS

Analysis of the results was performed using the Sigmaplot scientific graphing software (Jandel Corp.), the contrast sensitivity functions being plotted as probability of correct letter identification against $\log_{10}$ contrast. The contrast was calculated as the Weber fraction and expressed as a percentage, that is,

$$\frac{I_{\text{object}} - I_{\text{background}}}{I_{\text{background}}} \times 100\%$$

where I represents luminance in cd m^{-2}. Each set of results was modelled to an equation of the

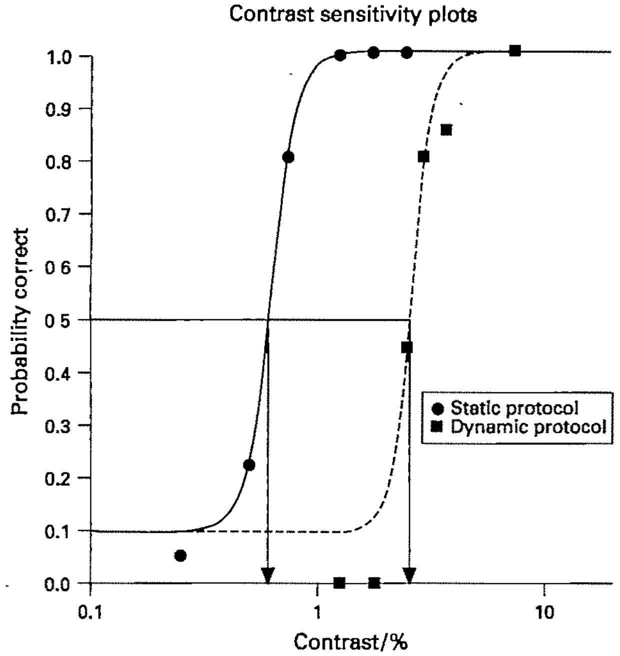

Figure 2 Contrast threshold. The curve fitted to the data is used to calculate the contrast at which the subject correctly identifies 50% of the letters displayed. This is defined as the contrast threshold.

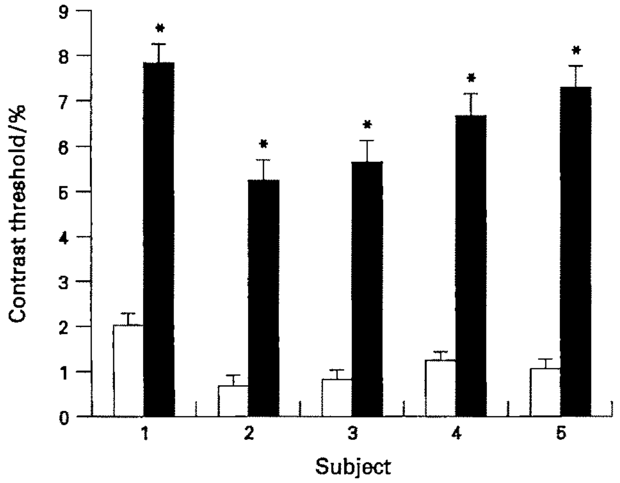

Figure 3 Results for the static protocol. Contrast thresholds are shown without isoflurane (open bars) and with 0.15% end tidal isoflurane (filled bars). The SEM is indicated. *Curve-fits significantly different at $P<0.05$.

general form:

$$P_c = \frac{0.9}{1+(kC)n} + 0.1$$

where P_c represents the probability of correctly identifying a letter at contrast C%. k and n are parameters whose values were determined in an iterative process based on the Marquardt-Levenberg algorithm. The 0.1 and 0.9 terms arise as the function has a minimum of 0.1 and a maximum of 0.1 + 0.9 = 1.0.

The relatively small number of results collected meant that the accuracy of the curve-fit was less certain at the ends of the function, but as only the threshold contrast was used in the comparison of results, this was not significant. Threshold contrast was defined as the contrast at which the subject correctly identified 50% of the letters.

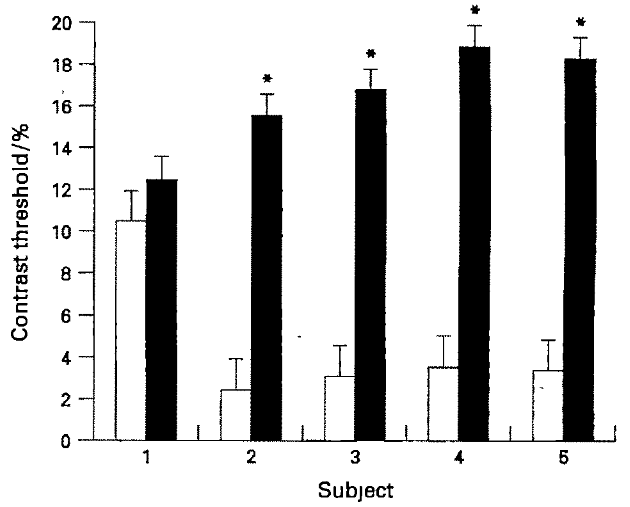

Figure 4 Results for the dynamic protocol. Contrast thresholds are shown without isoflurane (open bars) and with 0.15% end-tidal isoflurane (filled bars) for each subject. *Curve-fits significantly different at $P<0.05$.

STATISTICAL ANALYSIS

The standard error of the mean (SEM) was calculated for each contrast threshold. The F test was also used to test whether the curve-fits for the data obtained with and without anaesthesia for each subject were significantly different at the 5% level.

Results

The threshold contrast for each subject with or without isoflurane administration was obtained from a plot of the number of correct letter identifications at a particular contrast level (expressed as a percentage of the total letter presentations at that contrast level) against the contrast level. This is illustrated in figure 2.

The threshold contrasts for the five subjects are plotted in figure 3 for the static protocol and figure 4 for the dynamic protocol.

Isoflurane produced an increase in the threshold contrast of each subject in the static protocol. The increase ranged from 280 to 660% between subjects. Analysis of the curve-fits with the F test showed significance of the order of $P<0.05$ for each subject between the data obtained with and without 0.15% end-tidal isoflurane.

In the dynamic protocol, an increase in the threshold contrast with isoflurane was also seen in each subject. The increase ranged from 20% to 540%. F test analysis showed this to be significant at $P<0.05$ for four of the five subjects. In the subject without a significant performance decrease when isoflurane is administered (subject 1 in fig. 4), there appears to be a combination of a below average performance in the absence of isoflurane and an above average performance with isoflurane administration.

Discussion

The results show an increase in the threshold contrasts of all the subjects when isoflurane is administered to give an end-tidal concentration of 0.15%, for both the static and dynamic protocols. There are two possible reasons for this. The first is that the subject's contrast sensitivity may be affected by isoflurane administration. However, it is also possible that isoflurane may induce the subject to make more mistakes when typing in the letter on the keyboard, that is, contrast sensitivity remains unaffected, but input accuracy is reduced.

There are two reasons why it is believed that the effects of alterations in typing accuracy are minimal. First, there are only 10 letter responses that are allowed – if the subject does not pick one of these, he must repeat his choice until he does. This will have the effect of reducing typing errors, although admittedly not all possible errors. The second reason is based on an analysis of the results. If input accuracy were responsible for the change in threshold when isoflurane were administered, the plot of % correct *vs* contrast would be expected to retain the same sigmoid shape, but to be shifted down the % correct axis. This is because an effect on typing accuracy would be evident along the whole range of the function. However, this pattern is not observed – instead, the curve is shifted to the right, that is, along the contrast axis, implying that it is contrast sensitivity that is the affected factor.

Contrast sensitivity can therefore be confidently said to be a measure of recovery from anaesthetic sedation. In this series of experiments, no attempt was made to assess the dose-dependency of the effect, so it is not possible to comment on the sensitivity of the effect.

Contrast sensitivity may therefore be added to the list of other tests that can be used to measure anaesthetic sedation. The advantage of this technique is the relative simplicity of the equipment required and of the operation of the test – no measuring device needs to be attached to the subject, and the subject's instructions are easy to follow. The disadvantage of this method is that a fairly large number of results need to be obtained to gain an accurate measurement of contrast sensitivity threshold. In order for a full assessment to be made, some idea of dose-response would be required.

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Effects of nicardipine on ventriculo-arterial coupling in humans

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Summary

The ratio of effective arterial elastance (Ea) to left ventricular elastance (Ees) is an indicator of the coupling between ventricular properties and arterial load properties. Another criterion for the coupling between an energy source and its load is the principle of economical fuel consumption, or mechanical efficiency, which is defined as the ratio of stroke work (SW) to myocardial oxygen consumption per beat ($M\dot{V}O_2$). It has been revealed that SW of ventricular contraction is maximized when Ea/Ees=1, while mechanical efficiency is maximized when Ea/Ees=0.5. The purpose of the present study was to investigate the ventriculo-arterial coupling during hypertension, and the effects of nicardipine on this relationship in surgical patients using Ea/Ees and SW/$M\dot{V}O_2$ as indicators. Anaesthesia was maintained with isoflurane, nitrous oxide, and fentanyl. Radial artery pressure was displayed on a polygraph, and left ventricular end-systolic and end-diastolic volumes were determined by use of transoesophageal echocardiography. Ees was calculated as MAP/(ESVI-4), where MAP is mean arterial pressure and ESVI is end-systolic volume index. Ea was calculated as the ratio of MAP to stroke volume index (SVI). Stroke work index (SWI) was calculated as the product of MAP and SVI. $M\dot{V}O_2$ was assessed by estimating the ventricular pressure-volume area index (PVAI), which is expressed as the sum of SWI and the end-systolic potential energy index. Before (baseline), and 3, 10, 20, and 30 min after i.v. nicardipine (30 μg kg^{-1}), Ea/Ees and SWI/PVAI were determined in 14 surgical patients with intraoperative hypertension. Before nicardipine (during hypertension), Ea was almost equal to Ees, whereas Ea/Ees was significantly reduced to about 0.5–0.6 at 3, 10, and 20 min after nicardipine. SWI/PVAI was maximized and significantly greater than the baseline value at 3 min after nicardipine. These results suggest that, during hypertension, ventricular and arterial properties were so matched as to maximize SW at the expense of the work efficiency, whereas mechanical efficiency of ventricular contraction was maximized after nicardipine. (*Br. J. Anaesth.* 1998; **81**: 180–185)

Keywords: measurement techniques, elastance; heart, stroke work; heart, ventrico-arterial coupling; oxygen, consumption; monitoring, transoesophageal echocardiography; calcium channel block

There has been long-standing interest in understanding the interaction between the heart and vasculature. A number of studies[1–8] have been performed to answer the question: what is the optimal coupling between the ventricle and arterial load under physiological and pathological circumstances? Sunagawa and colleagues[1 2] theoretically predicted and experimentally validated in isolated canine heart that maximization of left ventricular stroke work (SW) occurs under physiological conditions. Other groups,[3–5 8] showed that the normal ventricle yields maximum SW against normal arterial afterload in anaesthetized open-chested dogs and cats. In contrast, using a simple analytical model for the interaction between the heart and vasculature, particularly with regards to the ratio of SW to ventricular oxygen consumption ($M\dot{V}O_2$), defined as mechanical efficiency, Burkhoff and Sagawa[6] concluded that SW of ventricular contraction is maximized when the ratio of effective arterial elastance (Ea) to left ventricular elastance (Ees) is 1, while mechanical efficiency is maximized when Ea/Ees=0.5. They also suggested that, under physiological conditions, ventricular and arterial properties might be adjusted more toward optimization of efficiency than SW. Asanoi, Sasayama and Kameyama[7] tried to extend these observations to humans and showed that in patients with normal heart function Ea/Ees was approximately 0.5, but in patients with moderate myocardial depression Ea was almost equal to Ees. Burkhoff and Sagawa[6] speculated that these discrepancies might be explained by the unphysiological conditions of isolated heart and instrumental, open-chest animal preparations. Nevertheless, it is not known whether regulation of the heart and arterial system during anaesthesia and surgery in humans is orientated towards maximizing work or efficiency. The ultimate goal of this investigation was to study the ventriculo-arterial coupling in patients under general anaesthesia with arterial hypertension and after treatment of the hypertension with nicardipine by using Ea/Ees and SW/$M\dot{V}O_2$ as indicators.

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Patients and methods

Fifty-four ASA class II patients scheduled for non-cardiac surgery agreed to participate in this study. They developed hypertension (systolic arterial pressure $\geq$150 mm Hg or diastolic arterial pressure $\geq$90 mm Hg) for at least 5 min after surgical stimulation. These patients had hypertension as part of their preoperative pathology; had no evidence of heart failure or other forms of heart disease; and were in normal sinus rhythm without conduction abnormalities. They were not taking cardiac active medications, but most of them were taking antihypertensive, mainly vasodilating drugs. Our study design was approved by the Hospital Committee on Human Study, and written informed consent was obtained from all patients. Patients were premedicated with i.m. atropine 0.5 mg and hydroxizine 50 mg 30 min before arrival in the operating theatre. Anaesthesia was induced with thiopental 3 mg kg^{-1}, and maintained with 50–65% nitrous oxide, 0.5–2% isoflurane, and increments of fentanyl. Vecuronium was given to facilitate tracheal intubation. Ventilation was controlled to maintain Pa_{O_2} above 13.3 kPa and Pa_{CO_2} at approximately 4.6–5.3 kPa.

DOSE-DEPENDENT EFFECTS ON SYSTOLIC ARTERIAL PRESSURE

To define the effective clinical dose of the drug that would produce a satisfactory initial lowering of arterial pressure, the dose-response relation for i.v. nicardipine was studied in 40 patients (male/female=16/24, age 48 [23–59] years old) who developed hypertension for at least 5 min after surgical stimulation. An i.v. bolus of nicardipine in the dose range of 0.5 to 50 μg kg^{-1} was administered over 15 sec, and systolic arterial pressure was measured before (baseline) and every minute after nicardipine by use of an automatic blood pressure device (Nihon Colin BP-203i, Komaki, Japan) until the peak effects of nicardipine were obtained. Forty data points obtained in 40 patients were plotted as nicardipine doses compared with the ratio of systolic arterial pressure at the peak effects of nicardipine to those at baseline (expressed as % of baseline). These data were converted to probits and the dose-response equation was calculated by least-square curve fitting.

CARDIAC HAEMODYNAMIC EFFECTS

Subsequently, the cardiac haemodynamic effects of i.v. nicardipine (30 μg kg^{-1}) were evaluated in 14 patients (male/female=7/7, age 60 [45–68] years old) who developed hypertension for at least 5 min after surgical stimulation. All 14 patients were scheduled for major surgical interventions that required invasive cardiovascular monitoring. After induction of anaesthesia, a 22-gauge cannula was inserted into a radial artery for measurement of the systemic arterial pressure and blood sampling, and a triple-lumen thermodilution pulmonary artery catheter was placed in a pulmonary artery through the right internal jugular vein. The transducer of the transoesophageal echocardiography device (TEE, Aloka UST-5233 S-5, Tokyo, Japan) was inserted orally into the oesophagus and advanced firmly into the stomach with upward tilting of the tip. A cross-section of the left ventricle was visualized by transoesophageal two-dimensional echocardiography and an M-mode echogram obtained at the maximum antero-posterior diameter. This method was identical to that described by Matsuzaki, Toma and Kusukawa.[9] The ECG was simultaneously recorded with the M-mode. Before (baseline), and 3, 10, 20, and 30 min after i.v. administration of nicardipine, cardiac haemodynamic variables were measured. Measurements included heart rate (HR), systolic-, diastolic-, and mean-arterial pressure (AP), cardiac output (CO), systolic-, diastolic-, and mean-pulmonary arterial pressure (PAP), mean pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and left ventricular end-diastolic (EDD) and end-systolic diameters (ESD). The EDD was obtained at the onset of the QRS complex of the ECG, and the ESD at the peak of the anterior wall motion.[10] Left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated from a previously validated Teichholz method.[11] As with the study of Asanoi, Sasayama and Kameyama,[7] stroke volume (SV), CO, EDV, and ESV were normalized for body surface area (SVI, CI, EDVI, and ESVI). Systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), fractional shortening (FS), and ejection fraction (EF) were derived using standard formulae. Arterial blood samples were obtained to measure isoflurane and nicardipine plasma concentrations. Concentrations of isoflurane in plasma were determined by gas chromatography (Shimadzu GC-4, Tokyo, Japan), and those of nicardipine were determined by use of high-performance liquid chromatography (Shimadzu LC-1, Tokyo, Japan). The lower limits of detection of the assay for isoflurane and nicardipine plasma concentrations were approximately 0.1 mg dl^{-1} and 1 ng ml^{-1}, respectively. Overall the coefficient of variation was between 5%–10% for both isoflurane and nicardipine measurements.

EFFECTS ON VENTRICULO-ARTERIAL COUPLING

To investigate coupling between the heart and arterial system in surgical patients, we estimated the slope of the left ventricular end-systolic pressure-volume relation (Ees), the slope of the arterial end-systolic pressure-stroke volume relation (Ea), stroke work index (SWI), and myocardial oxygen consumption ($M\dot{V}o_2$) using the cardiac haemodynamic data obtained in the second trial (tables 1 and 2). In the present study, we did not generate multiple pressure-volume loops under multiple preload or afterload conditions but, based on the work of Asanoi, Sasayama and Kameyama[7] evaluating the ventriculo-arterial coupling in normal subjects and cardiac patients, we estimated that V0, that is the left ventricular volume at theoretical pressure zero, is 4 ml m^{-2} in normal subjects. Thus, Ees was calculated as MAP/(ESVI-4) and Ea as MAP/SVI,[7] where MAP is mean arterial pressure, ESVI is end-systolic volume index, and SVI is stroke volume index. We also analysed the ventriculo-arterial matching by using another criterion for optimal coupling between an energy source and its load—that is, the principle of economical fuel consumption or mechanical efficiency.[6] In the case of the heart, the mechanical efficiency is defined as the ratio of SW to myocardial

Table 1 Cardiac haemodynamic effects of nicardipine assessed by radial artery and pulmonary artery catheters. HR, heart rate; AP, arterial pressure; SVI, stroke volume index; CI, cardiac index; PABP, pulmonary arterial blood pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure. *Significantly different from baseline ($P<0.05$), mean (SD) ($n=14$)

	Baseline	3 min	10 min	20 min	30 min
HR (beat min^{-1})	97 (18)	101 (20)	97 (17)	92 (17)	93 (16)
AP					
systolic (mm Hg)	144 (30)	111 (21)*	113 (23)*	117 (27)*	122 (21)*
diastolic (mm Hg)	87 (14)	64 (12)*	66 (11)*	67 (11)*	71 (10)*
mean (mm Hg)	111 (20)	85 (16)*	86 (14)*	87 (17)*	92 (16)*
SVI (ml $beat^{-1}$ m^{-2})	37 (7)	47 (8)*	43 (9)	42 (9)	40 (9)
CI (litre min^{-1} m^{-2})	3.6 (0 7)	4.8 (1.1)*	4.1 (0.8)*	3.9 (0.9)	3.8 (1.1)
PABP					
systolic (mm Hg)	29 (11)	32 (9)	30 (7)	26 (7)	26 (8)
diastolic (mm Hg)	16 (7)	17 (6)	14 (5)	13 (4)	14 (5)
mean (mm Hg)	23 (9)	25 (8)	22 (5)	20 (6)	20 (7)
SVRI (dyne sec cm^{-5} m^{2})	2376 (555)	1279 (324)*	1540 (414)*	1704 (407)*	1880 (503)*
PVRI (dyne sec cm^{-5} m^{2})	196 (118)	174 (74)	196 (61)	187 (96)	168 (89)
PCWP (mm Hg)	14 (6)	15 (6)	12 (5)	11 (6)	13 (6)
CVP (mm Hg)	8 (3)	9 (4)	9 (4)	7 (4)	8 (4)

Table 2 Cardiac haemodynamic effects of nicardipine assessed by transoesophageal echocardiography. HR, heart rate; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; SVI, stroke volume index; CI, cardiac index; FS, fractional shortening; EF, ejection fraction. *Significantly different from baseline ($P<0.05$), mean (SD) ($n=14$)

	Baseline	3 min	10 min	20 min	30 min
HR (beat min^{-1})	92 (18)	98 (22)	97 (18)	94 (19)	92 (17)
EDVI (ml m^{-2})	64 (21)	70 (18)	59 (20)	61 (19)	61 (25)
ESVI (ml m^{-2})	31 (15)	23 (17)	22 (13)*	24 (14)	25 (14)
SVI (ml $beat^{-1}$ m^{-2})	33 (12)	46 (11)*	37 (9)	37 (11)	36 (12)
CI (litre min^{-1} m^{-2})	3.0 (0 9)	4.4 (1.1)*	3.5 (0.9)*	3.4 (1.2)	3.3 (1.3)
FS (%)	28 (7)	39 (10)*	36 (12)*	34 (9)*	33 (8)
EF (%)	53 (12)	68 (12)*	64 (16)*	63 (14)*	61 (12)

oxygen consumption per beat ($M\dot{V}O_2$). Based on the work of Asanoi, Sasayama and Kameyama,[7] we approximated SWI as the product of MAP and SVI (SWI=MAP×SVI). $M\dot{V}O_2$ was assessed by estimating the ventricular pressure-volume area index (PVAI), which has been shown to be linearly related to oxygen consumption when basal inotropic state does not vary.[12 13] The PVAI is defined as the area on the ventricular pressure-volume (P-V) diagram circumscribed by the end-systolic and end-diastolic P-V relations and the systolic portion of the P-V trajectory. PVAI can therefore be expressed as the sum of SWI and the end-systolic potential energy index (PEI), which is represented by the area of the triangle defined by the end-systolic P-V relation, the end-diastolic P-V relation, and the isovolumic relaxation portion of the ventricular P-V trajectory (see fig. 1 of reference 6).

Data were presented as mean (SD). Statistical analyses were accomplished by one-way ANOVA with Scheffe *F* test. $P<0.05$ was considered to be statistically significant.

Results

DOSE-DEPENDENT EFFECTS ON SYSTOLIC ARTERIAL PRESSURE

After the i.v. bolus of nicardipine in the dose range of 0.5 to 50 μg kg^{-1}, systolic arterial pressure declined in a dose-dependent manner (fig. 1) and reached a nadir 2–3 min after injection. Complications such as severe hypotension or disturbances of atrioventricular conductance did not occur. The dose-response equation obtained in this trial—that is, probit= −0.97×log (dose)+7.01, indicates that nicardipine 6 μg kg^{-1} and 24 μg kg^{-1} produce 10% and 25% reduction in systolic arterial pressure.

CARDIAC HAEMODYNAMIC EFFECTS

The time course of the cardiac haemodynamic effects of nicardipine 30 μg kg^{-1} assessed by radial artery and pulmonary artery catheters are summarized in table 1, and those assessed by TEE in table 2.

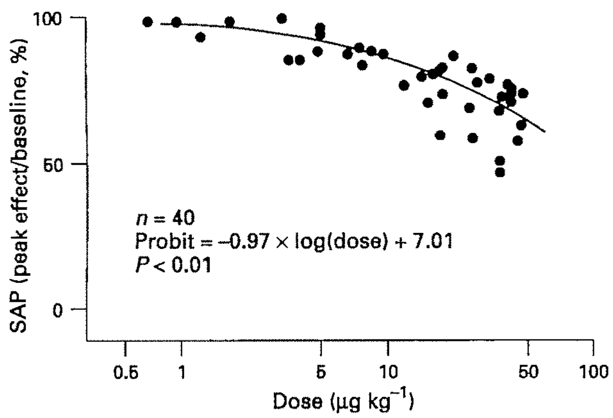

Figure 1 Dose-dependent effects of nicardipine on systolic arterial pressure (SAP) After the i.v bolus of nicardipine in the dose range of 0.5 to 50 µg kg^{-1}, SAP declined in a dose-dependent manner. The dose-response equation obtained in this trial—that is, probit=−0.97× log (dose)+7.01, indicates that doses of nicardipine 6 µg kg^{-1} and 24 µg kg^{-1} produce 10% and 25% reduction in SAP.

Three minutes after i.v. administration, nicardipine 30 µg kg^{-1} produced significant decreases in AP and SVRI, and significant increases in SVI, CI, FS, and EF. Nicardipine also produced a significant reduction in ESVI at 10 min after i.v. injection. After the peak effects, SVI, CI, ESVI, FS, and EF returned to the baseline values within 20 min, whereas AP and SVRI were significantly less than the baseline values even at 30 min after nicardipine administration. Other haemodynamic variables did not change significantly.

EFFECTS ON VENTRICULO-ARTERIAL COUPLING

Before nicardipine, Ea was almost equal to Ees (fig. 2, upper panel). Three, 10, and 20 min after i.v. administration, nicardipine 30 µg kg^{-1} produced small increases in Ees as compared with baseline values, but the differences did not reach statistical significance (fig. 2, upper panel). In contrast, there was a large and statistically significant decrease in the slope of Ea at 3, 10, 20, and 30 min after nicardipine (fig. 2, upper panel). As a result, Ea/Ees was significantly reduced from nearly 0.9 (baseline, a value obtained during hypertension) to 0.5–0.6 at 3, 10, and 20 min after nicardipine (fig. 2, lower panel). Both SWI and PVAI tended to decrease after nicardipine as compared with baseline values, but the differences did not reach statistical significance (fig. 3, upper panel). SWI/PVAI was significantly increased at 3 min after i.v. administration of nicardipine (fig. 3, lower panel).

TIME COURSE OF ISOFLURANE AND NICARDIPINE PLASMA CONCENTRATIONS

Isoflurane plasma concentrations (mean (SD)) at baseline and 3, 10, 20, and 30 min after nicardipine were 7.0 (1.9), 6.5 (2.2), 6.2 (2.4), 6.3 (2.3), and 6.2 (2.6) (mg dl^{-1}), respectively, suggesting that isoflurane plasma concentrations did not change significantly throughout the study period. Nicardipine plasma concentrations were 122 (34), 28 (7), 13 (8), and 8 (4) (ng ml^{-1}), respectively, at 3, 10, 20, and 30 min after i.v. administration of nicardipine 30 µg kg^{-1}.

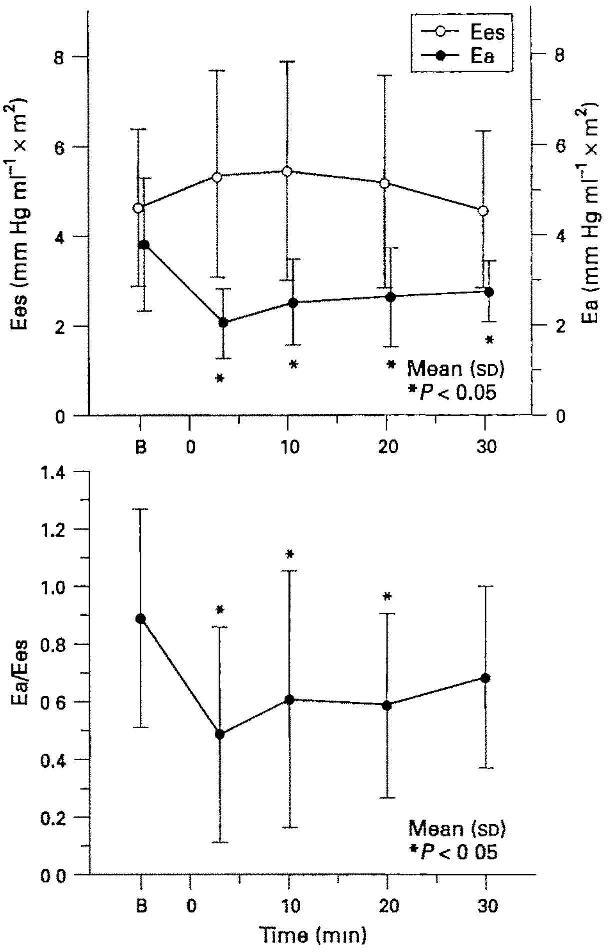

Figure 2 Effects of nicardipine on end-systolic ventricular elastance (Ees) and effective arterial elastance, (Ea) i v. administration of nicardipine 30 µg kg^{-1} did not produce significant changes in Ees as compared with baseline value (B), whereas there was a large and statistically significant decrease in the slope of Ea at 3, 10, 20, and 30 min after nicardipine (upper panel). As a result, Ea/Ees significantly reduced from nearly 0.9 (baseline, a value obtained during hypertension) to 0 5–0 6 at 3, 10, and 20 min after nicardipine (lower panel).

Discussion

The most important findings of the present study are that, during hypertension, ventricular and arterial properties were matched so as to maximize stroke work at the expense of the work efficiency, whereas mechanical efficiency of ventricular contraction was maximized after nicardipine. We investigated the ventriculo-arterial coupling in patients under general anaesthesia with arterial hypertension and after sufficient treatment of hypertension with nicardipine by using Ea/Ees and SWI/PVAI as indicators. As the arterial system and the left ventricle can be treated as elastic chambers that have volume elastance, Ea and Ees (at end-systole) respectively, the distribution of the volume between the two chambers can be determined by the ratio of their volume elastance values.[14] Thus, the ratio of Ea to Ees is an indicator of the coupling between ventricular properties and arterial load properties. Another criterion for the coupling between an energy source and its load is the principle of economical fuel consumption, or mechanical efficiency, which is defined as the ratio of stroke work (SW) to myocardial oxygen consumption per beat

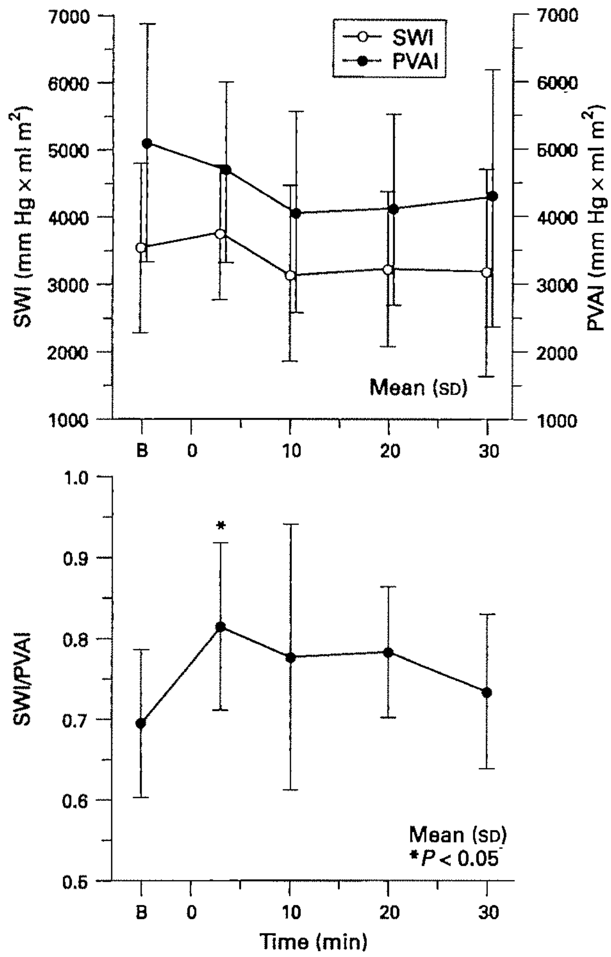

Figure 3 Effects of nicardipine on stroke work index (SWI) and ventricular pressure-volume area index (PVAI) Both SWI and PVAI tended to be reduced after nicardipine as compared with baseline value (B), but the differences did not reach statistical significance (upper panel). SWI/PVAI was maximized and significantly greater than the baseline value at 3 min after nicardipine (lower panel).

($M\dot{V}o_2$). $M\dot{V}o_2$ was assessed by estimating the ventricular pressure-volume area index (PVAI). Suga and his colleagues[12 13] have demonstrated that left ventricular PVA is linearly related to $M\dot{V}o_2$ per beat at a given heart rate with a stable inotropic background. As shown in figs. 2 and 3, Ea was almost equal to Ees before nicardipine (during hypertension), as predicted by Burkhoff and Sagawa[6] to achieve maximal SW. Ea/Ees was significantly reduced to 0.5–0.6 at 3, 10, and 20 min, and SWI/PVAI was maximized at 3 min after nicardipine to achieve maximal mechanical efficiency.

Based on the dose-response equation obtained in the present study (fig. 1), we predicted that the effective clinical dose of nicardipine for treatment of hypertension during anaesthesia and surgery would be 25–30 µg kg⁻¹. I.v. administration of nicardipine 30 µg kg⁻¹ produced significant reductions in AP, SVRI, and ESVI, and significant increases in SVI, CI, FS, and EF (tables 1 and 2). Other haemodynamic variables including PCWP, CVP, and EDVI did not change significantly. Isoflurane plasma concentrations did not change significantly throughout the study period excluding the possibility that changes in isoflurane concentration produced the changes observed. The direction and magnitude of changes in the haemodynamic variables produced by nicardipine were similar to those reported previously in patients with hypertension,[15] heart failure,[16] and ischaemic heart disease,[17] or in surgical patients with intraoperative[18] or postoperative hypertension.[19]

Among the haemodynamic variables, FS and EF are well accepted as clinically useful quantitative measurements of ventricular performance. However, their usefulness as measures of ventricular contractility are limited because both FS and EF are clearly afterload-dependent, and arguably preload-dependent.[20] In the search for a measure of ventricular function that is independent of loading conditions, Suga, Sagawa and Shoukas[21] showed in canine left ventricle that Ees is sensitive to changes in contractility. Sunagawa and colleagues[14] extended the ventricular pressure-volume analysis to include its interaction with the arterial bed and revealed that, given a constant heart rate, the arterial properties can be represented as an effective arterial elastance Ea. Although extremely useful for the evaluation of direct myocardial actions and peripheral actions of new drugs, the practical clinical application of Ees and Ea has been limited mainly for three reasons. First, easily applicable *in vivo* technology to measure ventricular volumes is not available in many clinical settings.[22] In the present study, we used TEE for measurement of left ventricular dimensions, and calculated left ventricular volumes by the formula of Teichholz and colleagues.[11] These and other groups[7 11 23] have reported the validity of echocardiography in evaluating left ventricular volumes. Second, determination of true end-systolic pressure (Pes) requires left ventricular or aortic pressure measurement. It has been demonstrated in humans[24] and predicted theoretically[1] that Pes in the arterial system can be approximated by mean arterial pressure (MAP). Thus, we assumed in the present study that left ventricular Pes is very close to MAP. The use of arterial pressure data obviates the potential added risk associated with left ventricular or aortic catheter placement.[25] Third, manipulation of arterial pressure in order to obtain different pressure-volume points may cause reflex inotropic changes, evidenced by increased or decreased heart rate, because of sympathetic activation or withdrawal.[20] A recently developed method for the estimation of Ees and V0 from analysis of single-beats indicated good correlation with measured values obtained by standard multiple-beat analysis.[26] In the present study, we did not generate multiple pressure-volume loops under multiple preload or afterload conditions, but we assumed that V0 is 4 ml m⁻²[7] and calculated Ees as MAP/(ESVI-4). By so doing, any single pressure-volume loop could allow us to estimate Ees without manipulation of arterial pressure.

Three and 10 min after i.v. administration, nicardipine 30 µg kg⁻¹ produced a small increase in Ees (fig. 2, upper panel). This slight increase in Ees might be partly baroreflex-mediated.[17] If so, these data indicate that direct cardiac actions of nicardipine are very minimal and transient. In contrast, there was a large and statistically significant decrease in the slope of Ea (fig. 2, upper panel). As Ea reflects afterload in the face of constant HR, left ventricular preload, and left ventricular contractility,[14] the observed significant reduction in Ea without significant changes in HR, PCWP, EDVI, and Ees, indicates a strong vascular selectivity of nicardipine (tables 1 and 2, fig. 2).

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British Journal of Anaesthesia 1998; **81**: 186–187

Influence of cuff volume on oropharyngeal leak pressure and fibreoptic position with the laryngeal mask airway

C. KELLER, F. PÜHRINGER AND J. R. BRIMACOMBE

Summary

We studied the size 4 laryngeal mask airway (LMA) to test the hypothesis that oropharyngeal leak pressure and fibreoptic position improves with increasing cuff volume. After LMA insertion, 50 anaesthetized adult patients had the cuff inflated in 5-ml increments to 40 ml. Oropharyngeal leak pressure was optimal at 15 ml and decreased at higher volumes. The fibreoptic position was optimal at 0–20 ml and deteriorated at higher volumes. Gastric insufflation was detected more frequently when the cuff volume exceeded 20 ml. We conclude that inflation of the size 4 LMA to the maximum recommended volume provides suboptimal conditions and that this value should be reduced from 30 to 20 ml. (*Br. J. Anaesth.* 1998; **81**: 186–187)

Keywords: equipment, masks anaesthesia; measurement techniques; fibreoptic

The laryngeal mask airway (LMA) forms a circumferential low pressure seal with the periglottic tissues and provides fibreoptic access to the vocal cords. The manufacturer recommends that the cuff is inflated with the minimal volume of air required to provide an effective seal,[1] but it is common practice to inflate the cuff with the maximum recommended volume, as illustrated in several trials.[2-4] There are no published data investigating the relationship between cuff volume and oropharyngeal leak pressure. In addition, the effect of increasing cuff volume on fibreoptic view is unknown. We tested the hypothesis that oropharyngeal leak pressure and fibreoptic position improve with increasing cuff volume up to the maximum recommended.

Methods

Fifty consecutive ASA I–II adult patients in whom the LMA was considered suitable were included in this study. Ethical committee approval and informed consent was obtained. A standard anaesthetic was given and routine monitoring applied. A size 4 LMA was used for all patients. Anaesthesia was induced with fentanyl 1–3 $\mu g\ kg^{-1}$ and propofol 2.5–3.5 $mg\ kg^{-1}$. Anaesthesia was maintained with 100% oxygen and a propofol infusion at 6–8 $mg\ kg^{-1}\ h^{-1}$ until testing was complete. A single experienced LMA user (1200 insertions) inserted/fixed the LMA according to the manufacturer's instructions. The pilot balloon was attached via a three-way tap to a 5-ml syringe and a calibrated pressure transducer. Cuff volumes were increased in 5-ml increments up to a maximum of 40 ml (10 ml more than recommended). Oropharyngeal leak pressure was determined by closing the expiratory valve of the circle system at a fixed gas flow of 3 litre min^{-1}, and noting the airway pressure in the anaesthetic breathing system at which gas leak occurred into the mouth. Air entering the stomach at the oropharyngeal leak pressure was detected by auscultation in the epigastrium. The view of the cords was scored fibreoptically from 1 cm above the mask aperture bars by a single investigator (FP) using an established scoring system: score 4, only cords; score 3, cords plus posterior epiglottis; score 2, cords plus anterior epiglottis; score 1, cords not seen, but function adequate.[5] Oropharyngeal leak pressures, intracuff pressures, gastric insufflation and fibreoptic scores were recorded at zero volume and after each additional 5 ml and when the patient was apnoeic. Statistical analysis was with paired *t* test (with Bonferroni adjusted probability) and chi-squared test. Significance was taken as $P<0.05$.

Results

All patients enrolled in the study were included in the analysis. There were no failed insertion attempts. The mean (range) for age was 37 (19–62) yr and mean (SD) weight and height were 75 (10) kg and 171 (19) cm respectively. The male:female ratio was 31:19. The results for oropharyngeal leak pressure, intracuff pressure, gastric insufflation and fibreoptic position with increasing cuff volume are presented in table 1. Oropharyngeal leak pressure was highest at 15 ml and declined thereafter, the difference becoming significant when comparing the oropharyngeal leak pressure at 20 and 25 ml (mean difference 1.5 cm H_2O, 95%CI 0.7, 2.2). Oropharyngeal leak pressure increased in 1 of 50 (2%) patients after the maximum recommended volume was exceeded. There was an exponential increase in intracuff pressure with increasing cuff volume. Gastric insufflation was detected more frequently when the cuff volume exceeded 20 ml (none of 250 [95%CI 0, 1] *vs* 4 of 200 [95%CI 1, 4], $P=0.02$). The oropharyngeal leak pressures at which gastric insufflation was detected

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Table 1 Oropharyngeal leak pressure (OLP), intracuff pressure (ICP), gastric insufflation (GI) and fibreoptic score (FOS) with increasing intracuff volume Values for OLP and ICP are mean (95% confidence intervals). Fibreoptic score 4=only vocal cords visible, 3= vocal cords plus posterior epiglottis, 2=vocal cords plus anterior epiglottis, 1=vocal cords not seen[5]

	Intracuff volume (ml)								
	0	5	10	15	20	25	30	35	40
OLP (cm H_2O)	12 (10, 13)	16 (14, 17)	19 (18, 21)	22 (20, 23)	22 (20, 23)	20 (19, 21)	19 (17, 19)	18 (16, 18)	17 (16, 18)
ICP (cm H_2O)	−29 (−34, −23)	15 (12, 17)	34 (30, 38)	58 (53, 63)	88 (80, 96)	126(118, 134)	183 (175, 190)	240 (231, 249)	306 (295, 316)
GI (*n*)	0	0	0	0	0	1	2	0	1
FOS (*n*)									
4	15	15	10	9	7	3	4	0	0
3	29	30	38	40	42	44	41	42	40
2	4	4	2	0	0	0	0	0	0
1	2	1	0	1	1	3	5	8	10
Median	3.143.18	3.16	3 14	3.1	2.94	2.88	2.68	2.6	

were 13–30 cm H_2O and only when the fibreoptic view was score 1. The fibreoptic score was highest at 0–20 ml and deteriorated thereafter, the difference becoming significant when comparing the fibreoptic score at 30 and 35 ml (P=0.03). In no patient did the fibreoptic view improve after 20 ml was exceeded. There was no significant correlation between age, height, weight and body mass index and either oropharyngeal leak pressure or fibreoptic score.

Discussion

These data suggest that the LMA functions better at sub-maximal cuff volumes and that the optimal volume for the size 4 LMA is 15–20 ml. Increasing cuff volume to 25 ml and above does not improve seal pressure or fibreoptic view, commonly results in a deterioration in both, and may increase the risk of gastric insufflation. In theory, the efficacy of the seal depends on the fit between the oval-shaped groove surrounding the glottis and the oval-shaped cuff of the LMA. The fibreoptic view depends on the alignment of the LMA bowl and glottis and the extent to which the epiglottis is downfolded during insertion. We postulate that the soft low volume cuff is better able to fit into the variable contours of the periglottic groove than the tense high volume cuff. It has been shown that increasing the cuff volume of the LMA displaces the larynx anteriorly.[4] It is also likely that at higher cuff volumes the wedge-shaped tip is displaced from the wedge-shaped hypopharynx causing proximal displacement of the cuff, movement of the epiglottis into the bowl and exposing the oesophageal inlet. This would explain the deterioration in fibreoptic view and the greater gastric insufflation at greater cuff volumes.

We conclude that inflation of the size 4 LMA to the maximum recommended volume provides sub-optimal conditions and that this value should be reduced from 30 to 20 ml. Researchers assessing efficacy of seal or fibreoptic position may have underestimated these values if the cuff was inflated to the maximum recommended volume.

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LABORATORY INVESTIGATIONS

Effect of L-lysine on nitric oxide production in ovine endotoxaemia[†]

K. G. ALLMAN, A. P. STODDART AND J. D. YOUNG

Summary

Excess production of nitric oxide contributes to the refractory hypotension associated with sepsis and is dependent upon precursor availability, L-arginine. Endothelial uptake of L-arginine by the y^+ transporter can be inhibited by another cationic amino acid, L-lysine. This study was undertaken to determine the effects of L-lysine in an anaesthetized ovine model of endotoxaemia in which nitric oxide production is known to be limited by L-arginine availability. The haemodynamic effects of i.v. L-lysine (500 mg kg^{-1}) were compared with those of a known inhibitor of nitric oxide synthase, N^G-nitro-L-arginine-methyl ester, L-NAME (25 mg kg^{-1}) and with control animals (n=6 per group). Serum nitrates, the stable end metabolite of nitric oxide production, were also measured. L-NAME administration caused a significant increase in systemic and pulmonary vascular resistance ($P<0.0001$), mean arterial pressure ($P<0.0001$) and a reduction in serum nitrate concentrations ($P<0.0001$). The administration of L-lysine had no effect on systemic or pulmonary vascular resistance, mean arterial pressure or serum nitrate concentrations. We conclude that the administration of L-lysine does not inhibit nitric oxide production in this model. (*Br. J. Anaesth.* 1998; **81**: 188–192)

Keywords: anaesthetic gases, nitric oxide; protein, amino acids, L-lysine; protein, amino acids, L-arginine; complications, endotoxaemia; complications, sepsis; model, sheep

Nitric oxide is a potent vasodilator synthesized from the semi-essential amino acid L-arginine by a family of enzyme isoforms.[1,2] Endothelial constitutive nitric oxide synthase (ecNOS) has a homeostatic role on blood vessel tone via the action of nitric oxide on soluble guanylate cyclase present in vascular smooth muscle. In sepsis or endotoxaemia, however, cytokine mediators induce expression of a calcium independent isoform of nitric oxide synthase (iNOS) which produces excessive uncontrolled amounts of nitric oxide.[3,4] This can cause refractory vasodilatation and hypotension leading to multi-organ dysfunction and death. Recently L-arginine analogues have been used as nitric oxide synthase inhibitors to increase vascular tone in human sepsis.[5,6] These agents act as non-specific inhibitors of nitric oxide synthase[7] and some (notably N^G-monomethyl-L-arginine, L-NMMA) also inhibit L-arginine uptake.[8] Studies in animal models of sepsis have recently suggested that non-specific nitric oxide synthase inhibition can have detrimental effects, possibly because of the co-inhibition of constitutive ecNOS.[9,10]

The majority of L-arginine transport into endothelial cells occurs via a saturable, low affinity, high capacity cationic amino acid transport system (y^+) which can be inhibited by other cationic amino acids such as L-lysine and L-ornithine.[8,11] The uptake of L-arginine by vascular endothelial cells may become rate limiting for nitric oxide production when excessive sustained production of nitric oxide occurs because of iNOS activation.[12–14] As intra-cellular stores of L-arginine appear to be sufficient for constitutive ecNOS production of nitric oxide, inhibition of L-arginine uptake could potentially allow selective inhibition of the iNOS enzyme whilst not affecting ecNOS activity.[15] This appears to occur in rodent models of endotoxaemia, but has not previously been examined in a large animal model.[14,16]

This study was undertaken to determine if excess nitric oxide production associated with ovine endotoxaemia could be reduced by the administration of L-lysine. A known nitric oxide synthase inhibitor, N^G-nitro-L-arginine-methyl ester (L-NAME), which has no effect on L-arginine transport, was used as a positive control.

Methods

These experiments were performed in accordance with United Kingdom Home Office regulations concerning experimentation on live animals.

ANIMAL PREPARATION

After an overnight fast 18 Soay sheep (10–24 kg) were anaesthetized with thiopental (12.5 mg kg^{-1}), intubated and ventilated to normocarbia with 60% oxygen in air. Anaesthesia was then maintained with halothane (1.5%) and a fentanyl infusion (2–4 $\mu g\ kg^{-1}\ h^{-1}$). A 16-gauge cannula was inserted into the left common carotid artery and a balloon-tipped thermodilution catheter (Abbott Critical Care, Chicago, USA) advanced into a pulmonary artery from the left internal jugular vein. The rumen was decompressed by gastrostomy and a urinary catheter inserted to measure hourly urine output.

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Animals were then placed in a sitting-recumbent position under a heated blanket to maintain normothermia. Saline (308 mMol) (10–15 ml kg^{-1} h^{-1}) was administered i.v. to maintain normovolaemia.

EXPERIMENTAL PROCEDURE

After a one hour period of stabilization, baseline measurements were taken and *Eschericha coli* endotoxin (Serotype 0127:B8, Sigma Chemicals, Poole) 2 μg kg^{-1} was administered i.v. over 30 min. After a further 2 h animals were randomly assigned to one of three groups of equal size (six animals per group). These groups received:

(1) L-lysine 500 mg kg^{-1} administered i.v. over 1 h followed by the same dose infused over 8 h,
(2) L-NAME 25 mg kg^{-1} administered i.v. over 1 h followed by the same dose infused over 8 h, or
(3) Saline (308 mMol) 50 ml administered i.v. over 1 h followed by 50 ml infused over 8 h.

L-lysine (Sigma Chemicals, Poole) and L-NAME (Alexis Corporation, Nottingham) were administered as the hydrochloride salt dissolved in 50 ml saline (308 mMol). L-NAME at a dose of 25 mg kg^{-1} has previously been shown to produce a reasonable degree of nitric oxide synthase block in ovine endotoxaemia,[17] and L-lysine 500 mg kg^{-1} was chosen after consultation with the pharmacy department of the John Radcliffe Hospital, Oxford, as a large dose is unlikely to cause directly toxic effects based on data from drug company development of total i.v. feeding regimens.

DATA COLLECTION

Animals were studied for a period of 10 h after endotoxin administration, to allow sufficient time for full induction of the inducible isoform of nitric oxide synthase.[3 4] Systemic and pulmonary arterial pressure, central venous and pulmonary arterial occlusion pressure and cardiac output (by triplicate cold saline (308 mMol) injection) were measured every 30 min for 5 h, then hourly for a further 5 h. At the same time intervals samples were taken for arterial blood–gas analysis (Radiometer ABL 330, Copenhagen, Denmark) and for the determination of serum nitrate concentrations.

NITRATE ANALYSIS

Blood samples for nitrate analysis were immediately centrifuged at 3000 rpm for 15 min and the plasma fraction frozen at -40°C for later analysis. Samples were analysed using a semi-automated modification of the Braman technique.[18] In brief, 1 ml of plasma was deproteinated by addition of 1 ml 0.1 mol $litre^{-1}$ zinc sulphate solution and centrifugation at 3000 rpm for 10 min. Aliquots (0.5 ml) were then injected into hot (85°C), acidic, 0.1 mol $litre^{-1}$ vanadium III chloride solution which reduces inorganic nitrate and nitrite to nitric oxide. This was then eluted in a constant stream of nitrogen and the nitric oxide concentration measured by a chemiluminescence analyser (Ecophysics CLD 700AL, Dürnten, Switzerland). Total serum nitrite/nitrate was calculated on-line using in-house developed software and nitrate standards. This technique has an intra-assay coefficient of variation of 2% and an inter-assay variation of 10%.

The nitro group of L-NAME interferes with nitrate determination by this method so a second technique was developed for analysis of samples from the L-NAME treated group. This was based on the Sigma quality control test procedure for nitrate reductase. 300 μl of plasma was added to 300 μl of pH 7.5 KH_2PO_4/K_2HPO_4 buffer, 50 μl of 2 mmol $litre^{-1}$ NADPH, 50 μl of 50 μmol $litre^{-1}$ FAD, and 50 μl of 1 unit ml^{-1} aspergillus nitrate reductase (all reagents from Sigma Chemicals, Poole). This was incubated at room temperature for 1 h, followed by the addition of 500 μl of 0.2 mol $litre^{-1}$ zinc sulphate solution and 70 μl 2 mol $litre^{-1}$ sodium hydroxide to deproteinate the sample. The resulting solution was analysed for nitrite content using a standard Greiss reaction.[19] The intra-assay coefficient of variation for this method is 2.2% with an inter-assay variation of less than 5%. Buffer and serum spiked with L-NAME were tested over a range of concentrations and no interference of nitrate/nitrite determination detected. The two methods were verified for concordance using serum from control animals and equivalent results obtained. Results for serum nitrite alone were consistently $\leq$0.6 μmol $litre^{-1}$ or undetectable and nitrate to nitrite conversion was $\geq$90%.

DATA ANALYSIS

Results are expressed as mean (SEM). Systemic and pulmonary vascular resistance were calculated using standard formulae and cardiac index was calculated using the following formula for ovine body surface area[20]:

$$\text{body surface area } (m^2) = 0.082 \times \text{body weight}^{2/3} \text{ (kg)}.$$

Treatment groups (L-NAME or L-lysine administration) were compared with the control group (normal saline administration) using a two factor repeated measures analysis of variance from the start of treatment onwards, and performed on a Macintosh LC II microcomputer running StatView II software (Abacus Concepts, Berkeley, California). Change in serum nitrate in the control group was assessed by one factor repeated measures analysis of variance.

A P value of less than 0.025 was taken to be significant to account for multiple analysis against the control group.

Results

Two animals died in the L-lysine treated group. Deaths occurred after a sustained period of low output cardiac failure and occurred at 450 and 500 min after endotoxin administration. They could not be attributed to a biochemical or hypoxic/pH related cause, nor were they typical of endotoxaemia. There were no deaths in the other two groups. For comparison of the L-lysine treated and control groups, statistical significance was calculated twice, once for the four animals surviving to the end of the study period and once for all six animals up to the last measurement before the first death (420 min after endotoxin administration). These results were equivalent and the latter figure is quoted.

CARDIOVASCULAR

The administration of endotoxin caused changes typical of acute endotoxaemia with a marked increase in pulmonary vascular resistance and a reduction in cardiac index. By 2 h, the start time for L-lysine or L-NAME infusions, haemodynamic variables had returned towards baseline levels and a typical sepsis-like syndrome of decreasing arterial pressure and systemic vascular resistance was developing.

The administration of L-NAME caused an increase in systemic and pulmonary vascular resistance ($P<0.0001$) and mean arterial pressure ($P<0.0001$) (figs. 1–3). Cardiac index decreased sharply at the start of L-NAME administration, but the overall reduction was not significantly different from the control group (fig. 4). L-lysine administration had no significant effect on systemic or pulmonary vascular resistance, mean arterial pressure or cardiac index (figs. 1–4).

SERUM NITRATES

In control animals mean serum nitrate concentration increased from a baseline value of 11.6 µmol litre^{-1} (SEM 1.2 µmol litre^{-1}) to 13.8 µmol litre^{-1} (SEM 1.8 µmol litre^{-1}) ($P<0.001$, one factor analysis of variance). L-NAME administration caused a decrease in mean serum nitrate concentration from 9.5 µmol litre^{-1} (SEM 0.7 µmol litre^{-1}) to 5.9 µmol litre^{-1} (SEM 0.2 µmol litre^{-1}) ($P<0.0001$ *vs* controls). In the L-lysine treated group mean serum nitrate concentrations increased from a baseline value of 11.4 µmol litre^{-1} (SEM 0.9 µmol litre^{-1}) to 13.8 µmol litre^{-1} (SEM 0.6 µmol litre^{-1}) and was not significantly different from the control group (fig. 5).

Discussion

Severe human sepsis is characterized by a hyperdynamic circulation and reduced systemic vascular resistance which can be refractory to conventional vasoconstrictor therapy. Nitric oxide synthase block has been demonstrated to increase vascular resistance

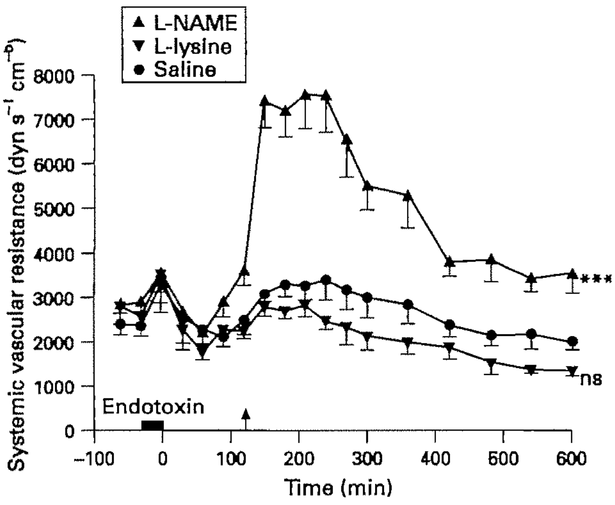

Figure 1 Change in systemic vascular resistance (dyn s^{-1} cm^{-5}) with time, n=6 per group (mean (SEM)). Arrow indicates start of L-NAME, L-lysine or normal saline infusion. (ns=no significant difference and ***$P<0.0001$ *vs* control group)

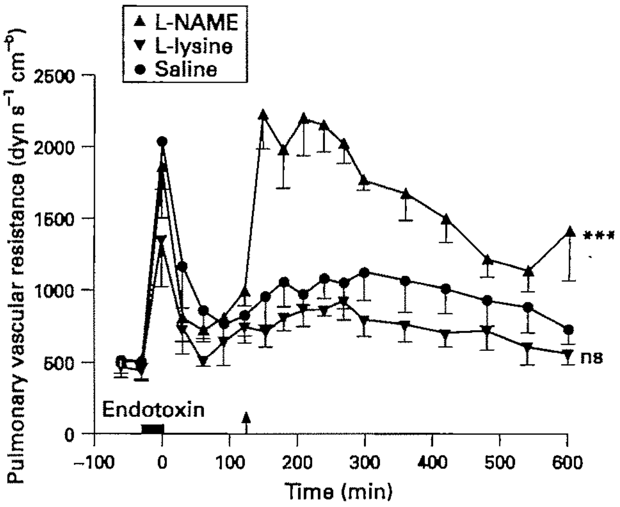

Figure 2 Change in pulmonary vascular resistance (dyn s^{-1} cm^{-5}) with time, n=6 per group (mean (SEM)). Arrow indicates start of L-NAME, L-lysine or normal saline infusion. (ns=no significant difference and ***$P<0.0001$ *vs* control group)

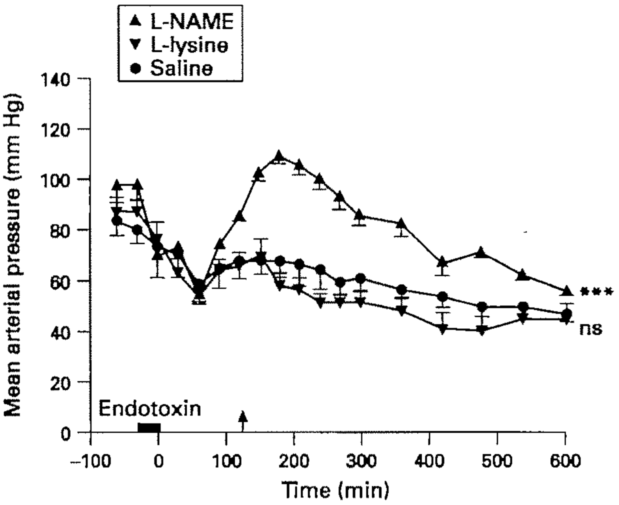

Figure 3 Change in mean arterial pressure (mm Hg) with time, n=6 per group (mean (SEM)). Arrow indicates start of L-NAME, L-lysine or normal saline infusion. (ns=no significant difference and ***$P<0.0001$ *vs* control group).

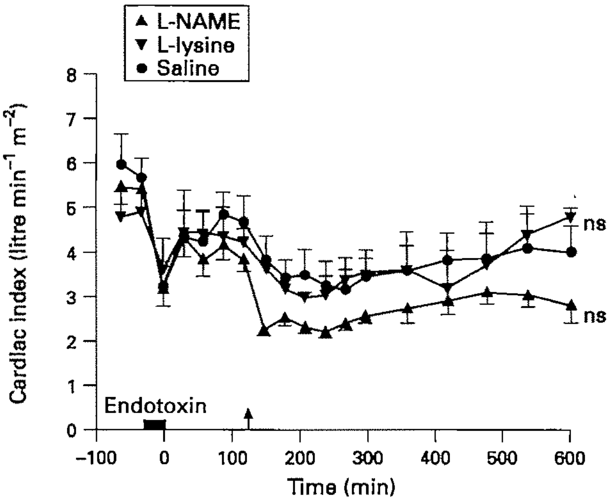

Figure 4 Change in cardiac index (l min^{-1} m^{-2}) with time, n=6 per group (mean (SEM)). Arrow indicates start of L-NAME, L-lysine or normal saline infusion. (ns=no significant difference *vs* control group).

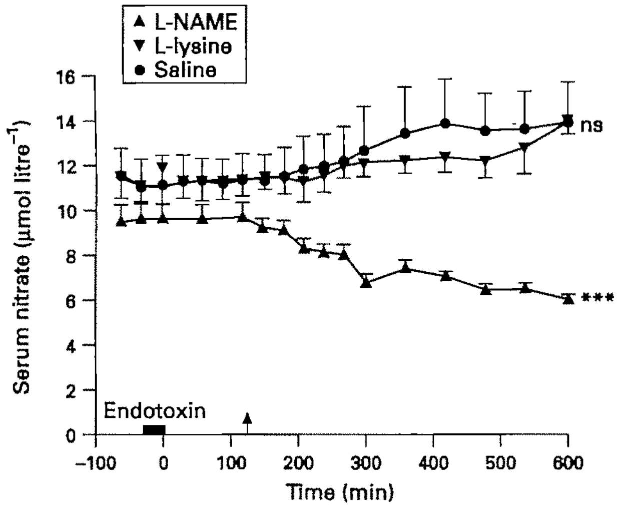

Figure 5 Change in serum nitrate concentration (µmol litre^{-1}) with time, $n=6$ per group (mean (SEM)). Arrow indicates start of L-NAME, L-lysine or normal saline infusion. (ns=no significant difference and ***$P<0.0001$ *vs* control group).

and systemic arterial pressure both in human[5,6] and animal[9,17] sepsis, but may have detrimental effects because of inhibition of the constitutive enzyme ecNOS.[9,10]

L-arginine uptake into endothelial cells occurs via a high affinity cationic amino acid transport system known as y^+. *In vitro* studies have demonstrated that the uptake of normal concentrations of L-arginine can be inhibited by other cationic amino acids such as L-lysine in concentrations of 1–10 mmol litre^{-1}.[8,11] By inhibiting L-arginine uptake rather than nitric oxide synthase production directly, it may be possible to inhibit the excessive production of nitric oxide by iNOS, whilst allowing low level constitutive production of nitric oxide by ecNOS to continue. This is possible because the K_m value for iNOS is some 10 times greater than that for the ecNOS enzyme.[21] Indeed, Bianchi and colleagues have demonstrated that a new tetravalent guanylhydrazone, CNI-1493, which inhibits cytokine-inducible L-arginine transport in murine macrophages, but does not affect constitutive nitric oxide production, conferred protection against lethal endotoxin challenge in mice.[16] Furthermore, Liaudet and colleagues have recently demonstrated that L-lysine (0.5 mmol kg^{-1} h^{-1} for 5 h) administered to endotoxin treated rats caused inhibition of nitric oxide production by iNOS, but not by ecNOS, and also tended to limit signs of organ dysfunction.[14] We have previously demonstrated that nitric oxide production in this ovine model of endotoxaemia is limited by L-arginine availability and we therefore postulated that the administration of exogenous L-lysine might reduce nitric oxide production in this large animal model.[22]

Administration of L-NAME, a recognized nitric oxide synthase inhibitor, caused a significant increase in mean arterial pressure and systemic/pulmonary vascular resistance compared with control animals. These results are similar to the effect of nitric oxide synthase inhibition in other studies of experimental endotoxaemia.[9,17] The haemodynamic effects were accompanied by a significant reduction in serum nitrate concentrations, the stable end metabolite of nitric oxide. The initial small offset in serum nitrate concentrations in the L-NAME treated group is probably because of differences in the assays used and would not affect the statistical analysis. More importantly, the reduction in serum nitrates in this group cannot be ascribed to an effect of the assay itself as the increased nitrate production noted in the control group was still present when these samples were re-analysed using the same aspergillus nitrate reductase assay. These data suggest that the haemodynamic changes after L-NAME administration resulted from a marked decrease in nitric oxide production.

The administration of L-lysine, on the other hand, had no significant effect on mean arterial pressure, systemic/pulmonary vascular resistance, cardiac index or serum nitrate concentrations indicating that L-lysine administration had no significant effect on nitric oxide production in this model.

Although serum concentrations of lysine were not measured, i.v. administration of L-lysine at a dose of 500 mg kg^{-1} (equivalent to 2.7 mmol kg^{-1}) should produce an extra-cellular concentration of at least 4 mmol litre^{-1}, a concentration which *in vitro* produces near maximal inhibition of L-arginine uptake.[11] Intra-cellular stores of L-arginine would not be sufficient to maintain nitric oxide production for the 10 h of the study period[11] and L-arginine production does not appear to occur from protein degradation.[23] Intra-cellular recycling of L-citrulline to L-arginine can occur via argininosuccinate synthetase and argininosuccinate lyase but this cannot sustain the increased nitric oxide production associated with endotoxin stimulation *in vitro*.[23,24] The disparity between Liaudet's and our own findings is interesting and may be because of a species difference. *In vivo* studies in rodents demonstrate that these animals respond to endotoxin by producing extremely large amounts of nitric oxide with a many fold increase in serum nitrate concentrations (peak 250–900 µmol litre^{-1}).[10,14] The increase in serum nitrates (and therefore of nitric oxide production) was more modest in our ovine model, which in this respect is closer to the changes found in human sepsis[25] and is one of the reasons that many authors consider ovine endotoxaemia to be one of the best models of human sepsis.[26] If nitric oxide production is increased only modestly then partial L-arginine uptake inhibition (coupled with some degree of intra-cellular recycling from L-citrulline) may not be sufficient to produce a clinically significant reduction in nitric oxide production. The dose of L-lysine used in the present study was some five times greater than that used by Liaudet and colleagues and was associated with a 33% late mortality. It is possible, therefore, that whatever mechanism was responsible for these toxic effects could mask haemodynamic changes resulting from a decreased nitric oxide production. This would not, however, explain the lack of effect on nitric oxide production as measured by serum nitrate concentrations.

It appears unlikely, therefore, that L-lysine or other cationic amino acids which act to reduce L-arginine uptake, could be used clinically to reduce nitric oxide production in human sepsis.

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Ratio of indocyanine green and glucose dilutions detects capillary protein leakage following endotoxin injection in dogs

I. SAKAI, H. ISHIHARA, T. IWAKAWA, A. SUZUKI AND A. MATSUKI

Summary

This study was designed to determine whether endotoxin-induced generalized capillary protein leakage can be detected using the ratio of indocyanine green (ICG) and glucose dilutions. Plasma volume determined by the ICG dilution method (Vd-ICG) and the initial distribution volume of glucose (IDVG) were assessed simultaneously before and after either the administration of lipopolysaccharide (LPS) 0.3 mg kg^{-1} or equal amounts of isotonic saline in two groups of eight dogs, using a one-compartment model after simultaneous infusions of both ICG 0.5 mg kg^{-1} and glucose 100 mg kg^{-1}. The IDVG has been shown to indicate the extracellular fluid volume of highly perfused organs including plasma. All post-treatment values decreased compared with the pre-treatment values ($P<0.05$), except Vd-ICG in the LPS group, even though the post-treatment total plasma protein concentration of the LPS group decreased significantly compared with the pre-treatment value ($P<0.05$). The post-treatment Vd-ICG/IDVG ratio of the saline group remained unchanged compared with that of the pre-treatment, and the post-treatment ratio of the LPS group increased significantly ($P<0.01$). It can be concluded that overestimation of the Vd-ICG can occur after endotoxin injection, which can be detected by simultaneous measurements of the Vd-ICG and the IDVG. (*Br. J. Anaesth.* 1998; **81**: 193–197)

Keywords. complications, endotoxaemia; protein, plasma; metabolism, glucose; measurement techniques, indocyanine green

Plasma volume often decreases in critically ill patients, caused by protein and water leakage from the capillary beds, particularly when a severe systemic inflammatory response has occurred during endotoxaemia.[1] Although the volume reduction can be diagnosed indirectly by measurements of packed cell volume, plasma protein concentration, and pulmonary artery wedge pressure (PAWP), these variables do not consistently parallel the plasma volume status.[2 3]

Indocyanine green (ICG) distributes throughout the intravascular compartment when administered i.v. and is metabolized exclusively in the liver. This dye has been used for estimating cardiac output (CO) and hepatic blood flow as well as plasma volume (Vd-ICG).[4] There is a good agreement between the ICG dilution method and red cell volume measurements using ^{51}Cr for calculation of blood volume in hospitalized patients.[4] However, as ICG binds to plasma proteins,[4] substantial systemic protein leakage from capillary beds may lead to an inaccurate estimation of plasma volume.[5] To our knowledge, there is only one report describing an inaccurate estimation of plasma volume in experimental endotoxaemia.[6]

Glucose cannot stay in the intravascular compartment and rapidly distributes throughout the intra- and extravascular compartment when administered i.v. Although ^{14}C-glucose distributes throughout the extracellular fluid (ECF) compartment,[7] glucose has not been used for dilution volumetry because its metabolism is believed to considerably modify its pharmacokinetic behaviour.[8] However, that belief should be reconsidered because recent radioisotopic studies have revealed that insulin does not affect extracellular glucose distribution kinetics or volumes in rats[9] or humans.[10]

The initial distribution volume for a given drug is composed mainly of the blood volume and the vessel rich group of tissues,[11] and that of glucose (IDVG) is affected appreciably by CO in critically ill patients[12 13] and in hypovolaemic dogs[14] and is not significantly influenced by glucose metabolism during measurements. The IDVG also correlates well with plasma volume in hypo- and hypervolaemic dogs,[15 16] which has been found to be similar to the initial distribution volume of sucrose.[17 18] Sucrose is not metabolized in the body when administered i.v. and has been used as an indicator for ECF volume measurement.[19] These findings suggest the IDVG as an index of the ECF volume status of highly-perfused tissues such as the heart, lungs, kidneys and liver as well as plasma volume, even though various substances in the blood may affect determination of plasma glucose concentrations and subsequently its pharmacokinetics.[20]

Assuming that the IDVG consistently indicates the ECF volume of highly-perfused tissues including plasma volume, regardless of the presence or absence of capillary protein leakage, an increase in the Vd-ICG/IDVG ratio would indicate the presence of protein leakage from capillary beds. The purpose of this study was to examine whether a change in the

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Vd-ICG/IDVG ratio occurred in endotoxin produced capillary protein leakage to the extravascular space.[1]

Materials and methods

The study design was approved by the Animal Care and Use Committee of our institution. Sixteen adult mongrel dogs of either sex (7.5–10.0 kg) were used and divided randomly into two equal groups, one of which received lipopolysaccharide (LPS, W.E.Coli 0127: B8, DIFICO, Detroit, USA). All dogs had their tracheas intubated after i.v. pentobarbital 30 mg kg^{-1}, and anaesthesia was maintained with a pentobarbital infusion at a rate of 2 mg kg^{-1} h^{-1}. Muscle relaxation was produced with i.v. pancuronium bromide at a rate of 0.06 mg kg^{-1} h^{-1} throughout the experimental procedure. Mechanical ventilation using a Servo 900C ventilator (Siemens-Elema AB, Stockholm, Sweden) was performed with room air to maintain the end-tidal carbon dioxide at 4.5–6.0% during the experiments.

The right femoral artery was cannulated for blood sampling and continuous arterial pressure monitoring. A pulmonary artery catheter (Baxter Healthcare Corp. Model 93A-741H-7.5F, Irvine, USA) was inserted through the left femoral vein and advanced until the tip was located in the pulmonary artery. An infusion of lactated Ringer's solution was continued at a constant rate of 4 ml kg^{-1} h^{-1}. After this preparatory procedure a stabilization period of 1 h was allowed. CO was then measured using a CO computer (American Edwards Laboratories 9520A, Santa Ana, USA) with 5 ml of chilled lactated Ringer's solution. The measurements were randomly performed during the ventilation cycle, conducted in duplicate and averaged. The coefficients of variation for repeated measurements were less than 10%.

After recording of mean arterial pressure (AP), heart rate (HR), mean pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), central venous pressure (CVP) and CO, both 0.5 ml kg^{-1} glucose (200 mg kg^{-1}) and 0.2 ml kg^{-1} ICG (2.5 mg kg^{-1}) (Daiichi Pharmaco Co. Ltd, Tokyo, Japan) were infused simultaneously by mixing them together in one syringe through the left femoral venous catheter over 30 s. A blood sample 3.5 ml was drawn for determination of plasma glucose and plasma ICG concentrations at times; immediately before, and 1, 2, 3, 4, 5, 7, 9, 11, 13, 15 and 20 min after the administration. A total of approximately 50 ml was sampled. Measurements of packed cell volume, haemoglobin, total plasma protein concentration, and arterial blood-gas analysis (Pa_{O_2}, Pa_{CO_2}, base excess, pH) were performed immediately before the administration. These data served as pre-treatment values.

Following all measurements and sampling the dogs of the LPS group received LPS 0.3 mg kg^{-1} diluted in 0.5 ml kg^{-1} isotonic saline, and those of the control group received isotonic saline 0.5 ml kg^{-1} i.v. Four hours later, the second administration of indicators and blood sampling were performed in the manner described previously. These data served as the post-treatment values. Plasma was separated immediately and measurements of glucose and ICG concentrations were completed within 1 h of sampling.

Plasma glucose concentrations were measured using the glucose oxidase method (Gluco-20 glucose analyser, Fuji Co. Ltd., Tokyo, Japan), and plasma ICG concentrations were determined using a spectrophotometric technique (U3200 Spectrophotometer, Hitachi Co. Ltd., Tokyo, Japan). Coefficients of variations were less than 2% for both plasma glucose between 2.0 and 20.0 mmol l^{-1} and plasma ICG between 0.1 μg ml^{-1} and 20 μg ml^{-1}, respectively.

The IDVG for each plasma glucose sample was calculated by using a one-compartment model (OCM) from the incremental plasma glucose decay curve between 3 and 7 min following glucose infusion. Vd-ICG was also calculated using a OCM from the plasma ICG decay curve between 3 and 11 min following ICG infusion. In a OCM the volume of distribution (Vd) is calculated as follows:

$$\mathrm{Vd} = \mathrm{dose}/\mathrm{C0}$$

where dose is the amount of drug administered, and C0 is the initial plasma concentration at time zero after instantaneous distribution but before the start of elimination. The IDVG and the Vd-ICG were determined using a least squares regression technique to find the line of the best fit. A non-linear multiple regression program (MULTI) was used on an NEC 9800 computer.[21 22] Akaike's Information Criterion (AIC)[23] was examined as described previously[9 13–18] to evaluate the exponential term of the pharmacokinetic model as follows:

$$\mathrm{AIC} = -\mathrm{N} \ln (\mathrm{SSQ}_w) + 2\,\mathrm{P}$$

where N is the number of data points, P is the number of parameters identified in the model, and SSQ_w is the weighted residual sum of squares. Low AIC values indicate a superiority of the selected model.

Data are presented as mean (SD) or median (range). Statistical comparison was made by Wilcoxon signed-rank test and Mann–Whitney *U*-test. $P<0.05$ is considered statistically significant.

Results

The post-treatment mean AP and HR of the LPS group decreased compared with the corresponding pre-treatment values ($P<0.05$) and the mean AP differed between the two groups ($P<0.05$). The post-treatment CO of two groups decreased compared with the corresponding pre-treatment value ($P<0.05$), but no significant difference was found between two groups (table 1).

Arterial blood-gas analysis revealed that the pH and base excess of the LPS group following treatment deteriorated, compared with pre-treatment values ($P<0.05$). These values remained unchanged in the control group, and a significant difference was observed between the two groups ($P<0.05$). The post-treatment total plasma protein concentration of the LPS group was significantly lower compared with the pre-treatment value ($P<0.05$), but not different from the control group (table 2). The value remained unchanged statistically in both groups during post-treatment.

As judged by AIC values[23] of the Vd-ICG and the IDVG calculated using a OCM, convergence was assumed in the Vd-ICG and the IDVG, even though convergence of the former was superior to the latter (table 3). Residual plasma ICG concentrations pre-

Table 1 Changes in the cardiovascular variables. Values are presented as median (range). PAP=pulmonary artery pressure, PAWP=pulmonary artery wedge pressure, CVP=central venous pressure, LPS=lipopolysaccharide, Before=before administration of isotonic saline or LPS, After=4 h after administration of isotonic saline or LPS. **P*<0.05 compared with Before-values, †*P*<0.05 compared with the control group

	Control group		LPS group	
	Before	After	Before	After
Heart rate (bpm)	174 (140–219)	160 (106–208)	163 (146–234)	144 (124–176)*
Mean arterial pressure (mm Hg)	145 (111–174)	146 (128–174)	144 (126–172)	124 (98–144)*†
Mean PAP (mm Hg)	19 (13–26)	21 (15–28)	21 (12–27)	22 (14–28)
Mean PAWP (mm Hg)	10 (4–22)	12 (8–20)	12 (8–18)	11 (8–18)
Mean CVP (mm Hg)	8 (6–11)	8 (6–9)	7.5 (3–8)	7 (4–8)
Cardiac output (ml kg^{-1} min^{-1})	184 (153–241)	128 (62–271)*	183 (144–257)	124 (66–175)*

Table 2 Changes in the laboratory variables. Values are presented as median (range). LPS=lipopolysaccharide, Before=before administration of isotonic saline or LPS, After=4 h after administration of isotonic saline or LPS. **P*<0.05 compared with Before-values, †*P*<0.05 compared with the control group

	Control group		LPS group	
	Before	After	Before	After
Haemoglobin (g dl^{-1})	14.5 (13.1–16.2)	14.5 (12.6–16.5)	12.7 (9.2–16)†	13.1 (9.2–17.1)
Packed cell volume (%)	41.7 (34.8–47.5)	43.3 (38.8–48 6)	37.2 (27.9–46.6)†	38 8 (27.8–59.6)
Total plasma protein (g dl^{-1})	4.9 (4.4–5.4)	4.5 (2.6–5.4)	5.5 (4.6–6.0)	4.3 (3.0–5.6)*
pH	7.38 (7.32–7.44)	7.34 (7.30–7.41)	7.36 (7.30–7.40)	7.26 (7.12–7.35)*†
Pa_{O_2} (kPa)	13.3 (12 0–17.7)	15.0 (11.3–19.5)	13.7 (13.5–19.9)	14.8 (11.2–20.7)
Pa_{CO_2} (kPa)	5.1 (4.3–6 0)	5.0 (3.9–6.3)	5.1 (4.4–5.8)	5.7 (4.5–8.0)
Base excess (mEq l^{-1})	–2.1 (–5.6–+3.3)	–4.2 (–9.8––2.3)	–3.4 (–6.8––1.6)	–8.1 (–11.7––6.4)*†
Urine output (ml kg^{-1} h^{-1})	1.5 (0.0–3.4)	3.9 (0.1–3.0)	1.0 (0.4–4 0)	0.2 (0.0–2.3)*†

sent before its second administration were 0.13 (0.08) μg ml^{-1} indicating that the first administration of ICG had been essentially cleared from plasma at that time. The mean pre-treatment plasma glucose concentration present before glucose infusion was 5.7 (0.6) mmol l^{-1} in the control group, and 5.8 (1.0) mmol l^{-1} in the LPS group. No correlation was found between the IDVG and plasma glucose concentrations present before glucose infusion (r=–0.03, n=32).

Post-treatment Vd-ICG and the IDVG decreased in the control group (*P*<0.05). In contrast, the post-treatment IDVG of the LPS group decreased similarly to that observed in the control group (*P*<0.05), but the corresponding Vd-ICG remained unchanged (table 3). The Vd-ICG/IDVG ratio of the control group was 0.42 (0.37–0.49) which remained unchanged following saline injection. The pre-treatment ratio of the LPS group was 0.45 (0.41–0.51), which increased to 0.55 (0.47–0.74) following LPS injection (*P*<0.05). The post-treatment ratio of two groups was different (*P*<0.01) (fig. 1).

Discussion

Kenneth, Birmingham and Harness[1] demonstrated that high vascular permeability began 4 h after a small dose of injected endotoxin. Considering this finding, a period of 4 h after endotoxin injection was allowed for determination of the post-LPS variables in this study.

A reduction in CO following endotoxin injection was similar to that following saline injection in this study. However, endotoxin injection, even in a small dose, caused significant effects on the cardiovascular system such as a decrease in mean AP and urine output as well as metabolic acidosis without apparent changes in CO.[24] Endotoxin injures the endothelium both directly and indirectly by increased cytokines and chemical mediators,[25] increases vascular permeability leading to water and plasma protein leakage to the extravascular compartment[1] and subsequently decreases plasma volume associated with haemoconcentration. In this study, endotoxin injection produced a significant decrease in total plasma protein concentrations associated with a statistically insignificant increase in packed cell volume. However, the post-treatment Vd-ICG of the LPS group remained unchanged compared with the pre-treatment value, suggesting possible overestimation of the Vd-ICG following the LPS injection. As judged by very low plasma ICG concentrations immediately before the second ICG administration in this study, modification by the residual ICG in plasma of the pharmacokinetic behaviour of ICG is negligible. Wang and colleagues[6] using septic rats reported packed cell volume and plasma volume using the ICG dilution method. The former was increased, suggesting a decrease in plasma volume, but the latter remained unchanged. Their findings are in agreement with ours.

In this study all data collection began at 3 min after the simultaneous glucose and ICG infusions in order to ensure the complete mixing within the initial distribution volume.[9 26–28] A two-compartment model (TCM) is generally required to analyse the pharmacokinetics of glucose.[9 26 27 29] However, the longer the interval after glucose administrations, the smaller the decrease in plasma glucose values, because amounts of glucose administered in this study were considerably

Table 3 Changes in the Vd-ICG and the IDVG. Vd-ICG=plasma volume determined by indocyanine dilution method, IDVG=initial distribution volume of glucose, BW=body weight, LPS=lipopolysaccharide. AIC=Akaike's information criterion,[23] Before=before administration of isotonic saline or LPS, After=4 h after administration of isotonic saline or LPS. *$P<0.01$ compared with Before-values, †$P<0.01$ compared with the control group

		Control group					LPS group				
		BW (kg)	Vd-ICG (ml kg^{-1})		IDVG (ml kg^{-1})		BW (kg)	Vd-ICG (ml kg^{-1})		IDVG (ml kg^{-1})	
	n		Before	After	Before	After		Before	After	Before	After
	1	9.0	48.3	41.1	100 0	94.4	8.0	61.3	53 3	120 0	72 0
	2	9.0	43.3	43.3	113.3	101.1	10.0	44 0	48.0	96.0	87.0
	3	9.0	43.3	41.1	117.7	104.4	8.0	47.5	51.2	113.7	88.7
	4	8.5	43.3	36.6	111.1	74.4	8.0	58.7	56.5	125.0	108.7
	5	7.5	46.6	40.0	102.6	80.0	8.5	48.2	44.7	117.6	80.0
	6	10.0	45.0	43.0	102.0	99.0	10.0	39.0	43.0	82.0	84.0
	7	8.5	52.9	43.5	108.2	94.1	10.0	45.0	41.0	109.0	87.0
	8	10.0	44.0	43.0	112.0	110.0	10.0	47.7	45.5	108.8	84.4
Median		9.0	44.5	42.1*	109.7	96.7*	9.3	47.6	46.8†	111.4	85.7*
Mean for AIC			–62.2	–54.3	–27.7	–25.4		–5.3	–65 8	–26.2	–31.9
SD for AIC			8 3	9.3	7.4	3.3		10.6	4.3	3.4	7.3

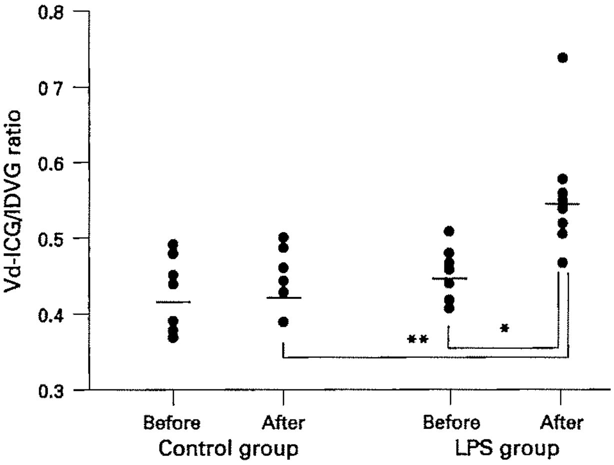

Figure 1 Changes in the Vd-ICG/IDVG ratio in the control group and the LPS group. Closed circles indicate data of each dog with median (horizontal bar). Vd-ICG=plasma volume determined by the indocyanine green dilution method, IDVG=initial distribution volume of glucose, LPS=lipopolysaccharide, Before=before administration of isotonic saline or LPS, After=4 h after administration of isotonic saline or LPS, *$P<0.05$ compared with the pre-Vd-ICG ratio, **$P<0.01$ between the control and the LPS groups.

smaller than those used in the conventional i.v. glucose challenge test. Therefore, an OCM was applied to each glucose decay curve using incremental plasma glucose values within 7 min after infusion. The IDGV calculated using an OCM tended to overestimate that of a TCM by approximately 5% in our experimental study.[15] In addition, administration of glucose itself has potential to expand the ECF volume by an acute increase in plasma osmolality. However, this modification would not be obvious because packed cell volume remained unchanged before and at 11 min after glucose challenge in this study.

Approximately 10% reduction of the Vd-ICG and 13% reduction of the IDVG were observed following saline injection in this study, even though lactated Ringer's solution 4 ml kg^{-1} h^{-1} was continuously infused throughout the experimental procedure, suggesting that the ECF volume of highly-perfused tissues including plasma volume decreased. The pre-treatment Vd-ICG was approximately 400 ml, if the weight of a dog was assumed to be 9 kg in this study. Blood samples taken from each dog totalled 50 ml for the pre-treatment value. Subsequently a reduction of plasma volume was approximately 30 ml, or 7.5% of total plasma volume if packed cell volume was assumed to be 39%. Presumably another factor might at least play a role in reducing the Vd-ICG and the IDVG. For the placement of an arterial and a pulmonary artery catheter in this study, invasive surgical techniques were used, which would produce a continuous small internal bleed at the operative site. We believe this factor would play a role, as after this study we performed the same experimental procedure as in the saline group using another eight dogs paying particular care to minimize continuous internal bleeding. The magnitude of these reductions was considerably lower compared with this study, and the Vd-ICG/IDGV ratio remained unchanged between these two saline groups. These data would support the notion that the dogs became hypovolaemic associated with a similar reduction in CO with time in both groups in this study.

In this study post-treatment CO and the IDVG were similar with or without LPS injection. This finding is supported by our previous observation that the IDVG correlates well with CO during hypovolaemia in dogs.[14] Thus, the post-treatment Vd-ICG/IDVG ratio in this study largely reflects changes in the Vd-ICG rather than those in the IDVG. Presumably the relatively high Vd-ICG/IDVG ratio indicates the presence of capillary protein leakage.

As judged by pre-treatment values of either packed cell volume or haemoglobin concentrations in this study, the saline injected dogs already had relative haemoconcentration compared with the endotoxin injected dogs; the inconsistent fluid volume status before treatment may modify the Vd-ICG/IDVG ratio. However, the ratio remained unchanged regardless of haemorrhage (30 ml kg^{-1}) or volume challenge (30 ml kg^{-1}) when the ratio was calculated using our previous experimental data.[15 16] Consequently, fluid volume status alone would not significantly affect the Vd-ICG/IDVG ratio.

As judged by pre-treatment values of HR, mean AP and CO in this study, the dogs would already have increased sympatho-adrenal activity, presumably by an infusion of pancuronium bromide as well as light anaesthesia with pentobarbital. However, our previous experimental study suggests that this hyperreaction is unlikely as judged by relatively low catecholamine concentrations during the same pentobarbital anaesthesia combined with pancuronium bromide.[30] These relatively high values of HR, mean AP and CO were observed consistently in our previous studies.[14–18] Presumably, the individual difference in cardiac responsiveness of each dog to the anaesthesia would affect these variables. Despite this variability, the IDVG, the IDVS and/or the Vd-ICG moved together consistently in the same direction following induced hypovolaemia or volume challenge in our previous studies.[14–18]

ICG leakage from the intravascular compartment has been observed not only in endotoxaemia, but also in several critical conditions such as pulmonary oedema and major burns.[5,30] This study supports the notion that a clinical misinterpretation or misdiagnosis of this phenomenon would have serious consequences in the critically ill patient. The single assessment of the Vd-ICG/IDVG ratio would allow us to evaluate this regardless of the fluid volume status. Additionally, the IDVG would have potential as an indicator of the central ECF volume status in the critically ill patient, even though its exact role over plasma volume remains to be investigated. In contrast with radioisotopic methods, it is simple and easy to perform.[12,13]

In conclusion, we have measured both the Vd-ICG and the IDVG of mongrel dogs following LPS injection. Following injection, we observed increased Vd-ICG/IDVG ratio associated with decreased IDVG. The results suggest that overestimation of plasma volume by the ICG dilution method occurs after injection, and that simultaneous measurements of these two estimates have potential for detecting capillary protein leakage in endotoxaemia as well as for evaluating fluid volume status.

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Effects of gelatin-based resuscitation fluids on platelet aggregation

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Summary

Fluid resuscitation aims to maintain intravenous volume without significant effects on haemostasis. Several different types of i.v. fluid are available for use in a patient who has suffered trauma, but there is evidence that some resuscitation fluids may affect primary haemostasis. We have compared the effects of two resuscitation fluids, Haemaccel and Gelofusine, on platelet aggregation *in vitro*. These resuscitation fluids are both based on gelatin but Haemaccel contains a high concentration of Ca^{2+} whereas Gelofusine does not. Their effects on platelet aggregation in whole blood, induced by a range of different agents, were determined using a platelet-counting technique. Both Haemaccel and Gelofusine prevented platelet aggregation induced by ristocetin ($P<0.05$, Mann–Whitney). In addition, Haemaccel proved to be a potent inhibitor of the platelet aggregation that occurred in response to all of the other agonists investigated: adenosine diphosphate, platelet-activating factor, collagen, a thromboxane A_2 mimetic (U46619) and epinephrine. The additional inhibitory effects of Haemaccel were largely, but not completely, attributable to its high Ca^{2+} content. Inhibition of platelet aggregation by ristocetin may indicate a mechanism by which Haemaccel or Gelofusine may contribute to impaired haemostasis. The presence in Haemaccel of high concentrations of Ca^{2+}, which is largely responsible for inhibition of the aggregation induced by other agents, may provide an additional means by which haemostasis could be impaired. (*Br. J. Anaesth.* 1998; **81**: 198–202)

Keywords: haemostasis; resuscitation fluids, Gelofusine; resuscitation fluids, Haemaccel; platelet aggregation; trauma

Treatment of hypovolaemic shock requires immediate restoration of the circulating volume by rapid infusion of i.v. fluid to restore and sustain blood volume, cardiac output, stroke volume, blood pressure, urinary output and oxygen delivery. Some resuscitation fluids contain the colloid gelatin; some also contain Ca^{2+}, which is intended to correct the decrease in ionized calcium that follows traumatic hypovolaemia.[1] The aim of adding calcium is to improve cardiac output by increasing and maintaining the force of contraction and also by increasing peripheral vascular tone.[2] The amount of calcium in the fluids is variable, and one gelatin-based solution, Haemaccel, contains a high concentration, 6.25 mM. Gelofusine is a gelatin-containing solution that does not contain Ca^{2+}.

There is concern that Haemaccel may interfere with primary haemostasis. In a previous study it was noticed that Haemaccel infusion to traumatized patients was associated with an increased bleeding time and pronounced blood loss.[3] An increased bleeding time in animals receiving Haemaccel has been documented,[4] and this was associated with significantly reduced adenosine-diphosphate-induced platelet aggregation in platelet-rich plasma derived from these animals. Haemaccel infusion to trauma patients can lead to hypercalcaemia, because of its high Ca^{2+} content.[5] It is also known that increasing the concentration of Ca^{2+} in blood plasma *in vitro* can impair the platelet aggregation that is a determinant of primary haemostasis.[6 7] It was therefore speculated that impaired haemostasis might be a consequence of the high concentration of Ca^{2+} in Haemaccel.[5] In the present study we have investigated the effects of Haemaccel and Gelofusine on the platelet aggregation induced by several different agonists. The agonists chosen were adenosine diphosphate (ADP), platelet-activating factor (PAF), collagen, a thromboxane A_2 mimetic (U46619), epinephrine and ristocetin. The effects of Haemaccel and Gelofusine on platelet aggregation were determined in whole blood using a platelet-counting technique.[8] The fluids were added to achieve a final concentration of 40% in blood, equivalent to an infusion of about 2 litres into a 70 kg person. As hypercalcaemia is also known to affect the platelet aggregation induced by some agents,[6 7] we also compared the effects of Haemaccel and Gelofusine with those of Ca^{2+} alone. We also carried out experiments in which Ca^{2+} had been added to Gelofusine. The whole blood was prepared using hirudin as the anticoagulant rather than the conventional citrate. This is because hirudin, unlike citrate, does not reduce the physiological level of ionized calcium in plasma, and additional Ca^{2+} can be added without affecting its ability to act as an anticoagulant.

Materials and methods

BLOOD COLLECTION

Venous blood was obtained from normal subjects who denied taking any medication in the 2 weeks before sampling. Blood was taken into a polypropylene

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syringe using a 19-gauge needle, and dispensed into a polypropylene tube containing Revasc (recombinant hirudin, final concentration 50 g ml^{-1}). The sample was routinely kept for 30 min at 37°C before testing.

Haemaccel (3.5% w/v polygeline) was purchased from Behring and Gelofusine (4% w/v succinylated gelatin) from B. Fraun Medical. Calcium chloride ($CaCl_2.6H_2O$) was obtained from Fisons, and sodium chloride (0.9% w/v) from Baxter Health Care. All platelet agonists were obtained from Sigma Chemicals except collagen (Hormon-Chemie) and ristocetin A sulphate (AL). Revasc (recombinant hirudin) was a gift from Ciba Geigy. The platelet fixative solution contained 150 mM NaCl, 4.6 mM Na_2EDTA, 4.5 mM Na_2HPO_4, 1.6 mM KH_2PO_4 and 0.16% w/v formaldehyde, pH 7.4.

PLATELET AGGREGATION

Platelet aggregation in whole blood was measured using the platelet counting technique described by Fox and colleagues.[8] A blood sample (292 µl) was mixed with 200 µl of the test solution (Haemaccel, Gelofusine or isotonic saline, previously warmed to 37°C) in a small polystyrene tube. After removing a 12 µl aliquot to 30 litre of fixative solution, 20 µl of a solution of an aggregating agent was added, and the sample placed in a water bath (37°C) and stirred (1000 r.p.m.). At appropriate time-points, 12 µl aliquots were removed from the sample and fixed as described. The number of single platelets in the fixed samples was measured using an Ultra-Flo 100 Whole Blood Platelet Counter. Platelet aggregation was expressed as the percentage fall in the number of single platelets compared with the starting count. The results are expressed as medians and interquartile ranges; in each case $n=7$, using blood from different volunteers. When the effects on platelet aggregation of additional Ca^{2+} were investigated, 10 µl of an isotonic solution of 100 mM $CaCl_2$ was added to saline (190 µl) or Gelofusine (190 µl) before adding the blood and aggregating agent. In the case of saline and Gelofusine this resulted in a concentration of ionized calcium in the blood of 2.6 mM and 2.5 mM respectively. This compared with a concentration of 2.8 mM when Haemaccel was used alone, and with 0.7 mM and 0.6 mM respectively when saline and Gelofusine were used alone. These measurements were performed using an AVL 988–4 analyser.

Statistical analysis was performed using a Mann–Whitney test. $P \leq 0.05$ was considered statistically significant.

Results

The effects of the various fluids on the platelet aggregation induced by a range of aggregating agents are shown in figs 1–6. The agonists used were ristocetin (1 mg ml^{-1}, fig. 1) adenosine diphosphate (ADP, 0.3 µM, fig. 2), collagen (1 µg ml^{-1}, fig. 3), platelet-activating factor (PAF, 0.3 µM, fig. 4), the thromboxane A_2 mimetic U46619 (0.3 µM, fig. 5) and epinephrine (100 µM, fig. 6). The timepoint after stimulation at which aggregation was measured was dependent on the agonist used. With ADP and PAF, aggregation was determined at 30 s (figs 2A and 4A) and 2 min (fig. 2B and 4B), as aggregation to low con-

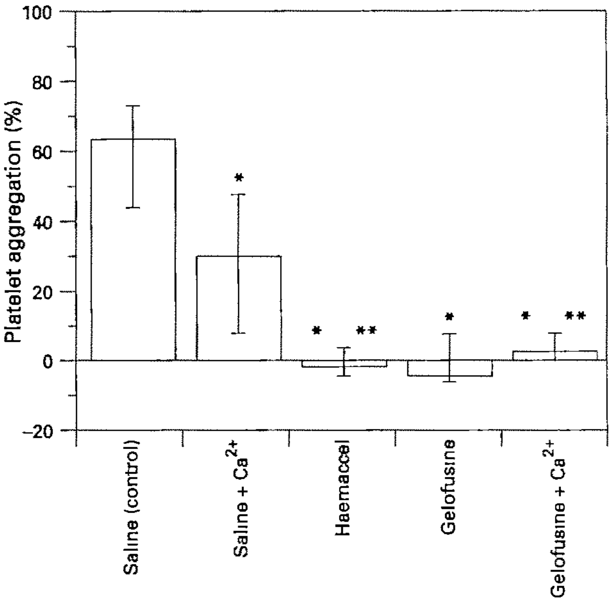

Figure 1 The effect of Haemaccel, Gelofusine and Ca^{2+} on the platelet agglutination induced by 1 mg ml^{-1} ristocetin at 4 min in hirudinized whole blood (*$P<0.05$ compared with saline, **$P<0.05$ compared with saline and saline + Ca^{2+}).

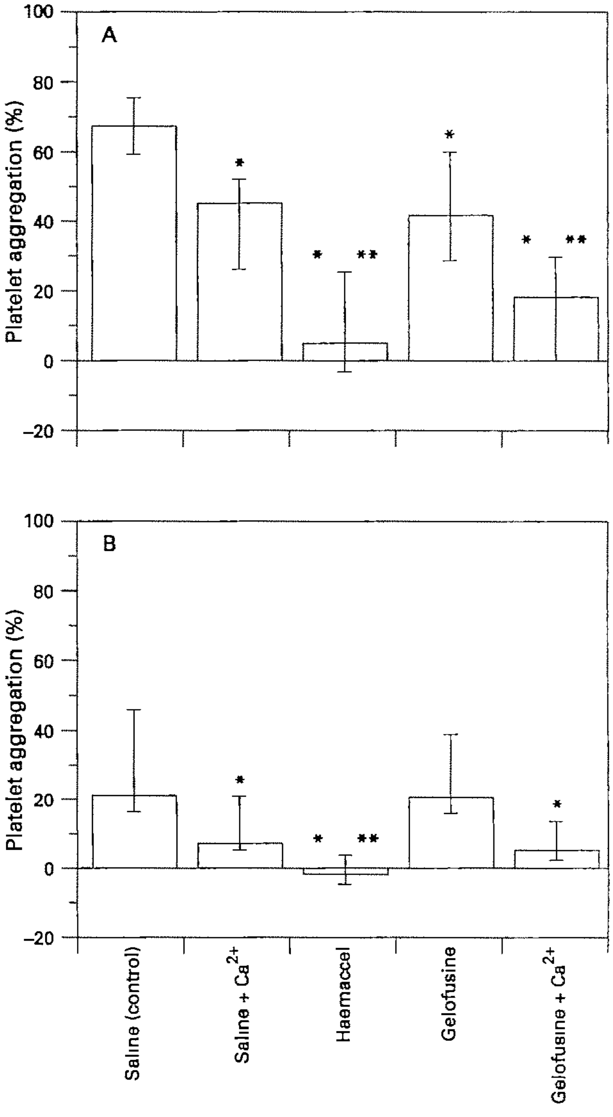

Figure 2 The effects of Haemaccel, Gelofusine and Ca^{2+} on the platelet aggregation induced by 0 3 µM ADP at 30 s (fig. 2A) and 2 min (fig 2B) in hirudinized whole blood (*$P<0$ 05 compared with saline, **$P<0$ 05 compared with saline + Ca^{2+}).

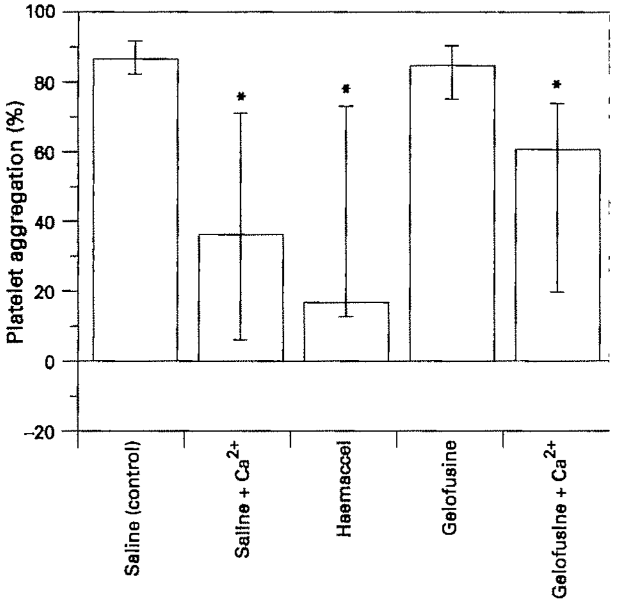

Figure 3 The effects of Haemaccel, Gelofusine and Ca^{2+} on the platelet aggregation induced by 1 g ml^{-1} collagen at 2 min in hirudinized whole blood (*$P<0.05$ compared with saline).

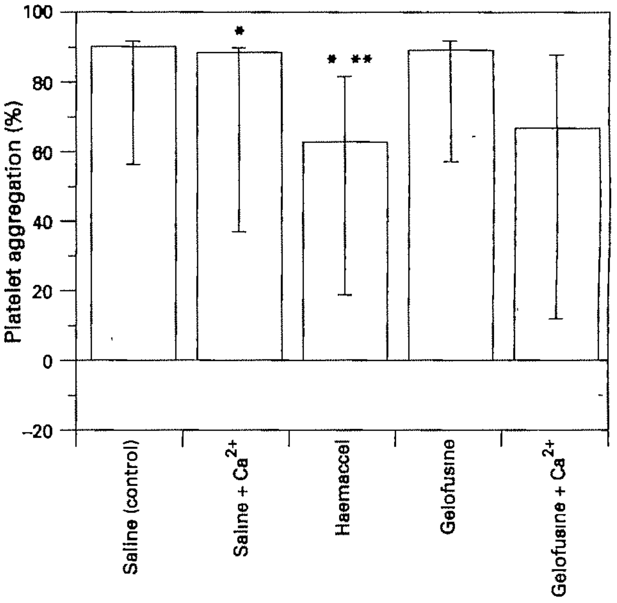

Figure 5 The effects of Haemaccel, Gelofusine and Ca^{2+} on the platelet aggregation induced by 0.3 μM U46619 at 2 min in hirudinized whole blood (*$P<0.05$ compared with saline, **$P<0.05$ compared with saline + Ca^{2+}).

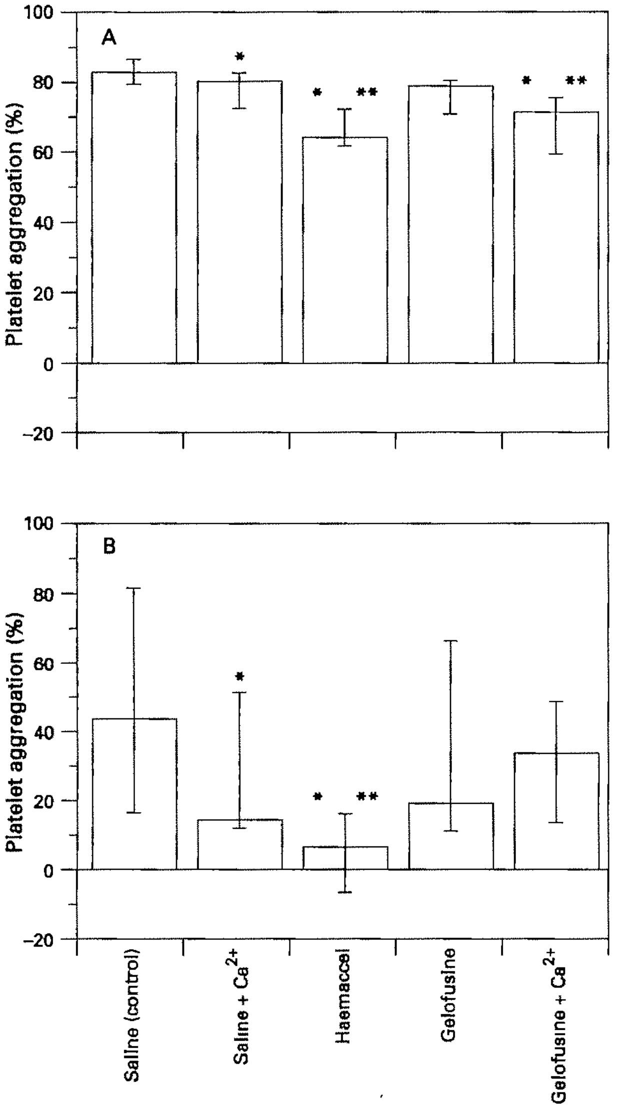

Figure 4 The effects of Haemaccel, Gelofusine and Ca^{2+} on the platelet aggregation induced by 0.3 μM PAF at 30 s (fig. 4A) and 2 min (fig. 4B) in hirudinized whole blood (*$P<0.05$ compared with saline, **$P<0.05$ compared with + Ca^{2+}).

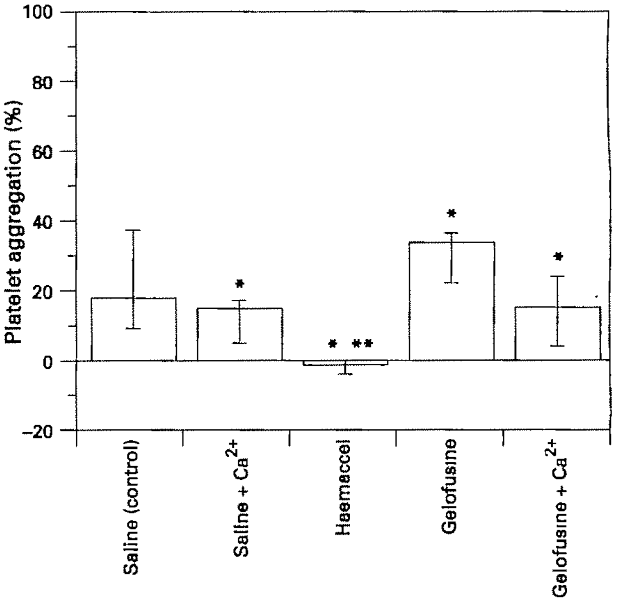

Figure 6 The effect of Haemaccel, Gelofusine and Ca^{2+} on the platelet aggregation induced by 100 μM epinephrine at 4 min in hirudinized whole blood (*$P<0.05$ compared with saline, **$P<0.05$ compared with saline + Ca^{2+}).

centrations of these agonists tends to be reversible. The response to the remaining agonists was measured when aggregation would normally be complete (collagen and U46619, 2 min; epinephrine and ristocetin, 4 min).

In the presence of Haemaccel or Gelofusine the platelet aggregation induced by ristocetin was totally prevented (fig. 1). Adding Ca^{2+} to the blood also inhibited the aggregation but this inhibition was only partial. The abolition of platelet aggregation in response to ristocetin by Gelofusine was not affected by increasing the Ca^{2+} concentration.

Haemaccel significantly inhibited the platelet aggregation that occurred in response to all of the other agonists (figs 2–6). Haemaccel also appeared to make the aggregation in response to ADP and PAF more reversible (figs 2 and 4). Adding $CaCl_2$ to the whole blood also resulted in a significant inhibition of platelet aggregation in response to all of the agonists studied. The inhibition seen with Haemaccel was always significantly greater than that seen with $CaCl_2$ alone, the only exception being when collagen was used as the agonist (fig. 3).

Except when ristocetin was used as the agonist, Gelofusine had only a slight effect on platelet aggregation. Significant inhibition of aggregation was seen in response to ADP at 30 s (fig. 2A), but this effect was lost by 2 min (fig. 2B). Gelofusine appeared to slightly potentiate the aggregation brought about by epinephrine (fig. 6).

Generally, there was less platelet aggregation with Gelofusine containing added $CaCl_2$ than with Gelofusine alone. This was the case in response to ADP (fig. 2), collagen (fig. 3), PAF (at 30 s, fig. 4A) and epinephrine (fig. 6). The results obtained for U44619 (fig. 5), and PAF (2 min, fig. 3B) show a trend towards inhibition but this did not reach statistical significance. The degree of inhibition seen with Gelofusine containing $CaCl_2$ was significantly greater than that observed with $CaCl_2$ alone for ADP (30 s, fig. 2A) and PAF (30 s, fig. 4B). Overall, the effect of Ca^{2+} on platelet aggregation was similar whether it was used alone or in combination with Gelofusine.

Discussion

One of the platelet agonists chosen for this investigation was ristocetin, which induces platelet aggregation through a mechanism involving von Willebrand factor and its receptor glycoprotein Ib on the platelet surface. Von Willebrand factor is also important in mediating adhesion of platelets to damaged vascular tissue, by forming a link between glycoprotein Ib and the damaged tissue. The aggregation induced in whole blood by this agent was prevented by Haemaccel and Gelofusine. Inhibition of ristocetin-induced aggregation by Haemaccel confirms earlier observations,[9 10] and extends the finding to the aggregation that occurs in whole blood as well as that in platelet-rich plasma. Platelets from patients with von Willebrand disease do not respond to ristocetin and this lack of response is associated with markedly reduced platelet adhesion to damaged vascular tissue and increased bleeding. There are indications that other, non-Ca^{2+}-containing, gelatin resuscitation fluids, as well as Haemaccel, may impair haemostasis. In a retrospective analysis of patients who had received oxypolygelatin before cardiopulmonary bypass, use of high doses of the fluid was associated with increased postoperative blood loss.[11] A recent prospective study, in which Gelofusine was infused into healthy volunteers, reported a significant increase in bleeding time.[12] Interference with haemostatic mechanisms involving von Willebrand factor could therefore be one way in which Haemaccel and Gelofusine, and presumably other gelatin-containing fluids, could increase bleeding and blood loss. An *in vitro* test of the effects of Haemaccel or Gelofusine on "clot quality" revealed that the presence of either agent led to production of clots that were more friable than normal clots.[13]

The other platelet agonists used in this investigation were ADP, PAF, collagen, U46619 and epinephrine. All these agents activate glycoprotein IIb/IIIa receptors on the platelet surface, leading to fibrinogen binding and platelet aggregation—another mechanism through which platelets contribute to primary haemostasis. Haemaccel inhibited the aggregation that occurred in response to all these agonists and increased the reversibility of the response. Gelofusine did not produce the same effect. The effect of Gelofusine on the aggregation induced by all agents other than ristocetin was slight, and although there was significant inhibition of the early aggregation induced by ADP this was matched by a slight potentiation of the aggregation induced by epinephrine. The different results obtained for the two gelatin preparations appeared to be largely, but not entirely, due to the presence of a high concentration of Ca^{2+} in Haemaccel.

There are reports that gelatin-containing resuscitation fluids can inhibit platelet aggregation[9 10] but, until now, there have been no direct comparative evaluations of the antiplatelet effects of Ca^{2+}-containing *vs* non-Ca^{2+}-containing preparations. Infusion of Gelofusine during cardiopulmonary bypass in man can lead to a reduced platelet response to Gelofusine[14], but it is not known how the fluids affect the different pathways leading to platelet aggregation.

Stibbe and colleagues studied the effects of several gelatin plasma substitutes on the platelet aggregation in platelet-rich plasma induced by ADP, collagen and epinephrine.[10] Haemaccel always inhibited the aggregation induced by all these agents whereas aggregation was enhanced by some other gelatin preparations. Our own experiments extend these observations to whole blood, emphasize that different results may be obtained with different types of gelatin colloids, and demonstrate that the presence of high concentrations of Ca^{2+} in Haemaccel increases the inhibition of aggregation seen using a range of platelet agonists. The inhibitory effects of Haemaccel on platelet aggregation induced by agents that act through glycoprotein IIb/IIIa and fibrinogen seem largely to be attributable to its high Ca^{2+} content, but some of the inhibitory effect may lie with its gelatin component, polygeline, which differs from succinylated gelatin, the gelatin component of Gelofusine.[15]

As Haemaccel inhibits the platelet aggregation induced by a range of agonists in addition to ristocetin, its administration could have an additional detrimental effect on primary haemostasis. On the other hand, agents that inhibit platelet aggregation can reduce the tendency to thrombosis, and in an animal model, platelet thrombus formation was significantly impaired after Haemaccel infusion.[16] Agents that specifically block platelet aggregation by interfering with the ability of fibrinogen to bind to glycoprotein IIb/IIIa receptors are being developed for use as antithrombotic agents in man.

We believe that further studies of gelatin-containing colloids are warranted to determine their potential for increasing bleeding after large-volume blood replacement. It might be important to balance this effect against the perceived need to restore calcium lost as a result of hypovolaemic traumatic shock. There may also be a case for further study of circumstances in which the inhibitory effects of such fluids on platelet aggregation could be beneficial. For example, an i.v. fluid with antiaggregatory properties might benefit trauma patients who have underperfused hypostatic capillary beds, by promoting blood flow and enhancing organ perfusion and tissue oxygenation. Similarly, inhibition of platelet aggregation could provide a degree of protection from thrombosis. However, whether these possible benefits would outweigh the potential for an increase in bleeding in the trauma patient remains to be proven.

Acknowledgement

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Effects of thiopental on airway calibre in dogs: direct visualization method using a superfine fibreoptic bronchoscope

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Summary

Induction of anaesthesia with thiopental sometimes causes bronchospasm. Although the mechanism by which thiopental induces bronchospasm may involve cholinergic stimulation, direct spastic effect and histamine release, the spastic effects of thiopental have not been comprehensively defined. In this study, we have assessed the effect of thiopental on *in vivo* airway smooth muscle tone using direct visualization method with a superfine fibreoptic bronchoscope as previously reported. Twenty-one mongrel dogs were anaesthetized with pentobarbital (30 mg kg^{-1}) and paralysed with pancuronium (200 μg kg^{-1} h^{-1}). The trachea was intubated with a tube that had a second lumen for insertion of the bronchoscope (od: 2.2 mm) to continuously measure bronchial cross-sectional area. The tip of the bronchoscope was placed between the second and third bronchial bifurcation of the right lung. The dogs were allocated to three groups of seven: group T, A+T, H+T. In group T, thiopental 0 (saline), 0.1, 1.0 and 10 mg kg^{-1} was given i.v. In group A+T, saline i.v., 5 min later atropine 0.1 mg kg^{-1} i.v., and 5 min later thiopental 10 mg kg^{-1} was administered. In group H+T, bronchoconstriction was produced with histamine 10 μg kg^{-1} i.v. followed by infusion at 500 μg kg^{-1} h^{-1}. Thirty minutes later, thiopental 0, 1.0 and 10 mg kg^{-1} were given. Arterial blood sampling was performed for measurement of plasma catecholamines and histamine. In group T, thiopental significantly reduced bronchial cross-sectional area (maximally by 28.7 (5.6% at 0.5 min after thiopental 10 mg kg^{-1}), which returned to the baseline in 3 min, while any changes in plasma concentrations of catecholamines and histamine were not observed except norepinephrine level at 1 min following thiopental 10 mg kg^{-1} i.v. Atropine pretreatment completely prevented thiopental-induced bronchospasm in group A+T. In group H+T, thiopental 10 mg kg^{-1} transiently but significantly decreases bronchial cross-sectional area. Therefore, the present study indicates that the mechanism of thiopental bronchospasm may result from cholinergic nerve stimulation. (*Br. J. Anaesth.* 1998; **81**: 203–207)

Keywords: anaesthetics i.v., thiopental; complications, bronchospasm; histamine; measurement techniques, fibreoptic bronchoscope

Induction doses of thiopental do not abolish airway reflexes and hence tracheal intubation sometimes causes bronchospasm.[1] Baker and colleagues[2] reported that induction doses of thiopental produced a significant decrease in the angle formed by the vocal cords. In addition they observed complete glottic closure in four of 14 patients. As the entire motor innervation to the laryngeal muscles is supplied by two branches of the vagus nerve: the superior and recurrent laryngeal nerves,[3] the reduction in angle between the vocal cords including laryngospasm may be caused by vagal stimulation by thiopental. Thiopental related allergic reactions may be partially because of bronchospasm, as thiopental causes histamine release from leucocytes.[4-6] Several *in vitro* studies[7 8] have also shown direct spastic effects of thiopental on tracheal smooth muscle. The use of thiopental in asthmatic patients is controversial. Shnider and Papper[9] reported that thiopental in itself did not cause bronchospasm in asthmatic patients, while Pizov and colleagues[10] described that both asthmatic and non-asthmatic patients receiving thiobarbiturates had a greater incidence of wheezing (45%, 13%, respectively) than did asthmatic and non-asthmatic patients receiving propofol (0%, 3%, respectively).

We have recently developed a new direct method for quantification of bronchial calibre using a superfine fibreoptic bronchoscope, and have shown that this direct method may be more specific than conventional measurements such as airway pressure, airway resistance or dynamic pulmonary compliance.[11-15] In the present study, we have used this method to evaluate the *in vivo* effects of thiopental on bronchial smooth muscles in dogs.

Methods

Our study design was approved by Animal Care and Use Committee of the University of Hirosaki School of Medicine. Twenty-one mongrel dogs (8–12 kg) were anaesthetized with pentobarbital 30 mg kg^{-1} i.v. and paralysed with pancuronium at 200 μg kg^{-1} h^{-1}. The tracheas were intubated with tubes (id: 7.0 mm, Univent tube, Fuji System, Tokyo) that have a second lumen for the insertion of a superfine fibreoptic bronchoscope. The lungs were mechanically ventilated

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using a volume-controlled respirator (Servo 900C) with oxygen and the end-tidal carbon dioxide maintained at 4.0–4.5%. The femoral artery was cannulated to monitor arterial pressure and to obtain arterial blood samples. The femoral vein was also cannulated to insert a Swan-Ganz catheter (Baxter Health Co., Tokyo) via its sheath to avoid potentiation of histamine-induced bronchospasm by flushing histamine from the dead space of a single i.v. catheter.

IMAGING AND ANALYSIS OF AIRWAY

We inserted a superfine fibreoptic bronchoscope (od 2.2 mm: AF type 22A, Olympus, Tokyo) through the second lumen of the tracheal tube placing the tip between the second and third bronchial bifurcation of the right bronchus in order to continuously monitor bronchial cross-sectional area at the third bifurcation. The image at the third bifurcation was printed out with a videoprinter (VY-170, Hitachi, Tokyo) after expiration and before inspiration. The printed image was imported into a Macintosh computer (Power Macintosh 7100/80 AV, Apple Computer Inc., California) using a scanner (Scan-Jet 4c, Hewlett Packard Co, Colorado) to measure the bronchial cross-sectional area with the NIH Image program, which is a public domain image processing and analysis program (Wayne Rasband, US National Institutes of Health, available from Internet by anonymous ftp from zippy.nimh.nih.gov or on floppy disk from NTIS, 5285 Port Royal RD., Springfield, VA 22161, part number PB93–504868).

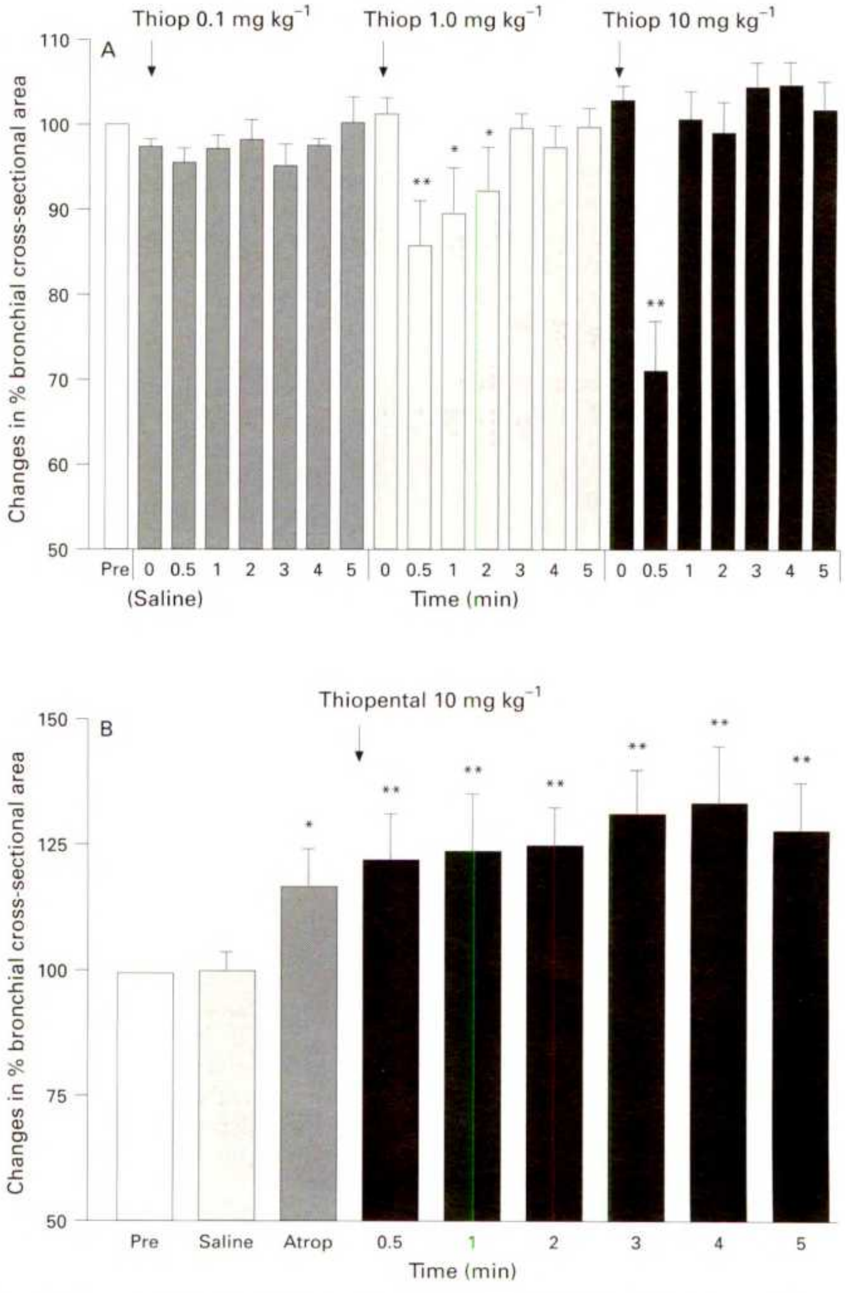

Figure 1 Effect of thiopental on basal bronchial cross-sectional area with (B) and without atropine (Atrop) pretreatment (A). Pre: before thiopental or saline i.v., Thiop: thiopental, * $P<0.05$, ** $P<0.01$ compared with Pre. All values are expressed as mean (SEM).

PROCEDURE 1: EFFECT OF THIOPENTAL ON THE BASAL AIRWAY TONE

Fourteen dogs were allocated to two groups: thiopental administration group (group T, n=7) and atropine-thiopental administration group (group A+T, n=7). One hour after the placement of a superfine fibreoptic bronchoscope, the experiment was started. This reduces the effect of pentobarbital induction as pentobarbital in itself decreases bronchial cross-sectional area.[13] However, dogs remained anaesthetized until the following procedure started (confirmed by electroencephalography in another 7 dogs).

In group T, after the basal bronchial cross-sectional area was measured, each thiopental dose: 0 (saline), 0.1, 1.0, 10 mg kg^{-1} was given in this order at 5-min intervals. The bronchial cross-sectional area was measured at 0.5, 1, 2, 3, 4 and 5 min after each thiopental dose i.v.

In group A+T, saline was given to confirm that the bronchoscope was well-fixed without any significant changes in bronchial cross-sectional area, 5 min later atropine 0.1 mg kg^{-1} was given i.v. and then 5 min later thiopental 10 mg kg^{-1} was administered. The bronchial cross-sectional area was measured at 0 and 5 min after atropine i.v. and 0.5, 1, 2, 3, 4 and 5 min after thiopental i.v.

PROCEDURE 2: EFFECTS OF THIOPENTAL ON HISTAMINE-INDUCED BRONCHOCONSTRICTION

Seven dogs were studied. The basal bronchial cross-sectional area measurement was performed before the induction of bronchoconstriction by continuous infusion of histamine at 500 µg kg^{-1} h^{-1} following a bolus injection of 10 µg kg^{-1} via pulmonary arterial catheter until the end of the experiment. Systolic arterial pressure was maintained above 80 mm Hg with fluid (lactate Ringer's solution: 50 ml kg^{-1}) and with continuous phenylephrine infusion at 0.5–2.0 µg kg^{-1} min^{-1}, the rate of which was dependent on systolic arterial pressure. Thirty minutes after the start of histamine infusion, thiopental: 0 (saline), 1.0, 10 mg kg^{-1} was given in this order at 5-min intervals. The bronchial cross-sectional area was measured at 0.5, 1, 2, 3, 4 and 5 min after each thiopental dose i.v. The bronchial cross-sectional area is presented as % of basal bronchial cross-sectional area.

PLASMA CATECHOLAMINES AND HISTAMINE ASSAY

Blood samples (6 ml) were taken through the arterial cannula at 1 and 5 min after each dose of thiopental i.v. and were immediately centrifuged at 3000 rpm for 10 min at −10 °C to separate plasma which was then frozen at −70 °C until assayed. The plasma concentrations of epinephrine and norepinephrine were determined by gas chromatography mass spectrometry in all groups. The coefficient of variation of the assay was 8.4 % for epinephrine and 11.3 % for norepinephrine. Plasma histamine concentrations in group T were measured by radioimmunoassay. The minimal detection limit was 0.2 nmol litre^{-1} and the intra- and inter-assay coefficient of variations were 7.2% and 7.8%, respectively. The antiserum showed no significant cross-reactivity with L-histidine, methyl-histamine, imidazole or methyl-imidazole.

STATISTICAL ANALYSIS

All data were expressed as mean (SEM). Data were analysed statistically using repeated measures analysis of variance followed by Fisher's protected least significant difference test using Stat View 2.0 for Macintosh. A P<0.05 was considered significant.

Results

PROCEDURE 1

Thiopental (>1.0 mg kg^{-1}) significantly reduced bronchial cross-sectional area, which spontaneously returned to the baseline within 3 min (group T, fig. 1A). With the exception of norepinephrine at 1 min after thiopental 10 mg kg^{-1} i.v., plasma concentrations of epinephrine, norepinephrine and histamine did not change significantly after thiopental i.v. (table 1). In group A+T, atropine significantly increased bronchial cross-sectional area, and this preadministration blocked thiopental-induced decrease in the bronchial cross-sectional area (fig. 1B). Moreover, thiopental significantly increased atropine-pretreated bronchial cross-sectional area (fig. 1B).

PROCEDURE 2

Histamine decreased the bronchial cross-sectional area by 34.1% (2.6 %) of basal bronchial cross-sectional area. The bronchial cross-sectional area decreased transiently but significantly after thiopental 10 mg kg^{-1} (fig. 2). Plasma catecholamines did not change (table 2).

Discussion

The present study demonstrates that thiopental transiently but significantly increased basal bronchial smooth muscle tone, which was completely inhibited by atropine pretreatment. Several reports[2,16] suggest that thiopental may increase upper airway reflex sensitivity to produce laryngospasm. This finding supports the notion that thiopental increases vagal tone to produce bronchospasm.

Table 1 Changes in plasma catecholamine and histamine concentrations 1 and 5 min following thiopental (T) i.v., mean (SEM). ** P<0.01 compared with before thiopental

		T 0.1 mg kg^{-1}		T 1.0 mg kg^{-1}		T 10 mg kg^{-1}	
	Before	1 min	5 min	1 min	5 min	1 min	5 min
Norepinephrine (pg ml^{-1})	121 (27)	158 (31)	136 (32)	143 (24)	151 (35)	240 (75)	186 (41)
Epinephrine (pg ml^{-1})	159 (15)	129 (13)	127 (23)	119 (14)	122 (19)	167 (22)	131 (10)
Histamine (nmol litre^{-1})	1.7 (0.2)	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)	1.9 (0.2)	1.9 (0.3)	1.8 (0.2)

Table 2 Changes in plasma catecholamine concentrations 1 and 5 min after thiopental (T) i.v. in presence of histamine (H) infusion at 500 $\mu g\ kg^{-1}\ h^{-1}$, mean (SEM). H30: 30 min after the start of histamine infusion

			T 1.0 $mg\ kg^{-1}$		T 10 $mg\ kg^{-1}$	
	H30	Saline	1 min	5 min	1 min	5 min
Norepinephrine ($pg\ ml^{-1}$)	237 (91)	202 (57)	321 (122)	306 (140)	453 (296)	293 (137)
Epinephrine ($ng\ ml^{-1}$)	3.78 (1.53)	3.16 (1.18)	7.82 (5.91)	4.84 (2.64)	7.38 (6.37)	16.5 (15.9)

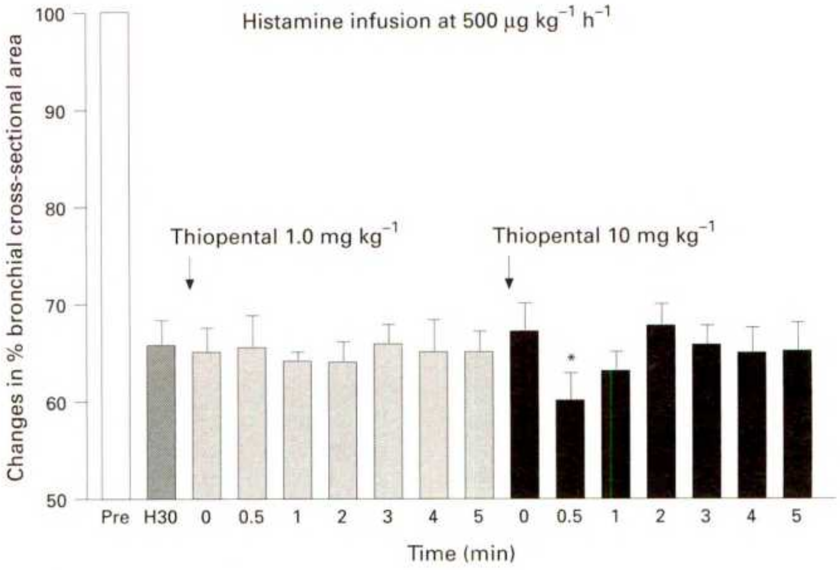

Figure 2 Effect of thiopental on histamine (H)-induced bronchoconstriction assessed by changes in bronchial cross-sectional area. Pre: before start of H infusion. H30: 30 min after the start of H infusion, * $P<0.05$ compared with H30. All values are expressed as mean (SEM).

In vitro studies indicate that thiobarbiturates, but not oxybarbiturates, directly produce airway smooth muscle contraction[7] which may result from the production of thromboxane A_2.[8] However, our previous report[13] showed that pentobarbital, an oxybarbiturate, increased bronchial smooth muscle tone. Moreover, the present study shows that thiopental-induced bronchospasm was completely blocked by atropine. Therefore, the production of thromboxane A_2 by thiopental may not be the primarily cause of bronchospasm *in vivo*.

Hirshman and colleagues[4] reported that thiopental-caused anaphylactic shock which may be because of histamine release from leucocytes. They also showed that thiopental induces histamine release in human skin mast cells.[5] In addition, Lorenz and colleagues [6] found increases in plasma histamine concentrations after i.v. administration of thiopental even in normal subjects. These findings suggest that histamine release may be involved in the mechanism of thiopental-induced bronchospasm. However, in the present study, as the plasma concentration of histamine did not change after i.v. thiopental, histamine release may not contribute to bronchospasm.

As thiopental inhibits sympathetic neural outflow,[17] it may cause bronchospasm.[18] However, in the present study, plasma level of catecholamines were not altered by thiopental i.v. with and without histamine infusion that increased plasma catecholamine concentration. Therefore, it is unlikely that sympatholytic effect of thiopental caused the bronchospasm in the present study.

In the present study, after atropine administration, thiopental unexpectedly produced a relaxant effect. Yamakage and colleagues[19] reported that thiopental inhibits voltage sensitive Ca^{2+} channels in porcine tracheal smooth muscle cells. It has been suggested that block of Ca^{2+} channels causes airway relaxation.[20] Taken together, the relaxant effect of thiopental following vagal denervation might be because of inhibition of Ca^{2+} influx.

In conclusion, the present study indicates that thiopental should be used carefully in patients with hyper-reactive airway as thiopental produced and worsened bronchospasm via vagal stimulation, and that atropine might protect from thiopental-induced bronchospasm.

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Pharmacological evidence for different alpha$_2$-adrenergic receptor sites mediating analgesia and sedation in the rat

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Summary

Alpha$_2$-adrenergic agonists given intrathecally result in antinociception and intracerebroventricularly (ICV) in sedation. To examine whether different alpha$_2$-adrenergic receptor subtypes differentially mediate antinociception and sedation, we measured the relative potency of three alpha$_2$-adrenergic agonists, dexmedetomidine (DMET), clonidine (CLON) and UK-14.304 (UK), after spinal and ICV administration. Each agonist was given either alone or in the presence of systemically administered yohimbine, which acts as a competitive alpha$_2$-antagonist in unanaesthetized rats. Intrathecal delivery of the agonists alone resulted in a dose-dependent antinociceptive effect (ED$_{50}$ (nmol): DMET=1.2, UK=1.7, CLON=5.6) with little sedative effect at the lower doses. Yohimbine pretreatment resulted in a rightward shift of the dose-response curves (DMET>CLON>UK). ICV alpha$_2$-adrenergic agonists produced a dose-dependent sedation (ED$_{50}$ (nmol): DMET=10.5; UK=28.7; CLON=126), with little antinociceptive action. Again, yohimbine pretreatment produced a right shift of the ICV sedation dose-response curves (UK>DMET>CLON). Thus, we conclude that the spinal analgesic effects of DMET, CLON and UK appear to be mediated by two sites. After ICV delivery, DMET, CLON and UK appear to act at a common supra-spinal site to produce sedation and this site resembles that acted upon by UK in the spinal cord. (*Br. J. Anaesth.* 1998; **81**: 208–215)

Keywords: receptors, adrenergic; sympathetic nervous system, clonidine; anaesthesia, depth; analgesic techniques, subarachnoid; rat

Alpha$_2$-adrenoceptor agonists produce powerful dose-dependent analgesia in animals[1, 2] and in humans[3, 4] when delivered into the intrathecal space. This analgesia is believed to result from an agonist interaction with presynaptic alpha$_2$-adrenergic receptors located on small primary afferents, which decreases the release of transmitter.[5–8] In addition these agonists are thought to interact with postsynaptic alpha$_2$-adrenergic receptors on projection neurons, hyperpolarizing the cell by increasing potassium conductance through Gi coupled K$^+$ channels.[9]

In addition to their subarachnoid analgesic activity, alpha$_2$-agonists produce dose-dependent sedation and EEG synchronization at supraspinal sites. The mechanism for the sedative response is believed to be similar to the analgesic action and is mediated through postsynaptic alpha$_2$-adrenoreceptors and inhibitory G proteins.[10–12] Microinjection studies have pointed to several brainstem sites, including the locus coeruleus,[11] which may subserve these effects. After spinal delivery, sedation is occasionally observed and is considered to reflect supra-spinal redistribution of the spinally delivered agent.[13]

Over the past years, it has been become apparent that there are several subclasses of the alpha$_2$- adrenergic receptor. At least three different subtypes: 2A, 2B and 2C have been described based on pharmacological properties. Cloning studies in rat and human tissue confirmed that several distinct subtypes exist.[14–19] In recent studies, we have found that alpha$_2$-adrenergic agonists exert their antinociceptive action at two sites, each having different yohimbine sensitivities.[20] Interestingly, at high spinal doses, one class of agonists appears to be associated with sedation while the other is not.[20] This suggests the possibility that supra-spinal sedation may be mediated by distinct alpha$_2$-adrenergic receptor subtypes. To determine if the different effects are mediated by sites with different affinity for this antagonist, we examined the effects of three spinal and intracerebroventricular (ICV) administered alpha$_2$ -adrenergic agonists alone and in the presence of systemically delivered yohimbine. The efficacy of a competitive antagonist, yohimbine, is proportional to its potency for the alpha$_2$-adrenoreceptor site. Thus differences in the antagonist's efficacy in reversing equieffective doses for analgesia or sedation of the alpha$_2$-adrenoreceptor agonists (clonidine, dexmedetomidine or UK 14.304) would suggest different receptor subtypes are involved in each response. In addition by using prazosin, a competitive antagonist, which predominantly inhibits alpha$_1$-adrenoceptor mediated effects, the observed antinociceptive or sedative activity could be localized to the alpha$_2$-receptor. Alternately, a similar dose-response shift for analgesia and sedation for the three agonists in the presence of yohimbine would provide pharmacological evidence that the stimulation of a similar alpha$_2$-adrenergic receptor subtype results in both, analgesia and sedation. The rationale for the use of the dose-ratio analysis has been more extensively reviewed elsewhere.[21, 22]

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Materials and methods

Animal surgery and testing procedures were approved by the institutional animal care committee of the University of California, San Diego. All procedures were performed according to these guidelines. Rats (male Sprague–Dawley, Harlan Industries, Indianapolis, IN, USA; 300–350 g) were implanted with intrathecal catheters and thereafter kept in separate cages on a 12-h light–dark cycle and given water and food *ad libitum*. Each rat was implanted as described below with an intrathecal catheter or an ICV cannula, or both. Animals were randomly assigned to treatment groups. The animals were anaesthetized and killed after the experiment was completed.

ANIMAL PREPARATION

For the spinal delivery of study drugs animals were prepared with intrathecal (i.t.) catheters in a modified version of techniques described previously.[23] Only animals with normal motor function after i.t. placement were used in the following experiments. ICV cannula insertion was performed using a modified version of the technique of Moron, Stevens and Yaksh.[24] Briefly, before surgery animals were anaesthetized with halothane (2–3% in 50% oxygen/air), breathing spontaneously via mask ventilation. For ICV cannulation a cranial burr hole (0.5 mm lateral to the sagittal suture and 0.5 mm caudal to the coronal suture, adjacent to the bregma) was made. The ICV cannula (23-gauge stainless steel: 15 mm in length) was lowered 3 mm beyond the dura into the left lateral ventricle. The cannula was fixed with cranioplastic cement to three stainless steel bone screws. After all surgical procedures, a recovery period of five days was allowed before starting the injection series.

ICV/IT INJECTION

Drugs were administered by a microinjection syringe attached to the indwelling catheters via a length of calibrated PE-90 tubing. For the i.t. studies, drugs were injected in a volume of 10 µl followed by 10 µl normal saline to flush the catheter. For ICV injections, the drug was delivered in a volume of 10 µl followed by 2 µl of saline to flush the cannula.

TEST MEASURES

For each drug, the following test measures were obtained before drug delivery and at 5, 10, 15, 20, 30 min after drug delivery.

Antinociception

The threshold for thermal stimuli was assessed by an observer blinded to the drug injected either ICV or i.t. using a technique previously described.[25] Each animal was placed in a Plexiglas cage (9×22×25 cm) on top of a glass plate with a surface temperature maintained at 30 °C by a feedback-controlled heater fan. The animal was left on this surface for at least 15 min before any stimulation to allow for proper adaptation. The thermal stimulus was manoeuvred under the glass to focus the projection bulb on the plantar surface of the paw. Initiation of the current to the halogen bulb started a timer. Bulb current was automatically terminated when paw elevation was sensed by photo diodes or when an interval of 20 s (cut-off time) had passed. Aiming of the focused stimulus was reliably accomplished by a mirror attached to the stimulus which permitted visualization of the undersurface of the paw. Light beam intensity was monitored by a measurement of bulb current and the stimulus intensity was calibrated daily by assessing the temperature change after 10 s sensed by an underglass thermocouple (T1/2=0.2 s). The intensity of the light was adjusted and maintained at baseline latencies of 10.2 s (0.6 SEM). Withdrawal latency to the nearest 0.1 sec were measured for both paws. The first measurement was made on both hind paws, the response latencies averaged and counted as baseline score (time 0). Tests were then made at 5, 10, 15, 20, 30 min after drug delivery.

Sedation

To score the behavioural changes before and during treatment of the animal, a sedation index was used. The index consisted of five behavioural parameters which have been shown to be blocked by opioids in a dose-dependent manner.[25] These measured responses included: pinna reflex, cornea reflex (both evoked by light touch of the surface of pinna or cornea with a small piece of PE-10 tubing), evoked movement (startle reflex evoked by tapping on the cage wall), signs of spontaneous movement (for example, grooming, chewing, ambulating) and assessment of the righting reflex. Each parameter was scored as follows: 0=normal (brisk pinna/cornea reflex response or startle reflex; spontaneous movement within 30 s of the assessed time-point; righting reflex was performed immediately after turning the animal on its back); 1=attenuated (touch with tubing for pinna or cornea reflex or knocking on cage wall does result in a slow reflex behaviour and has to be repeated, touch or knocking has to be repeated at least twice) or 2=completely absent (no reflex was shown after touching cornea three times or pinna both sides, no startle behaviour was displayed after knocking against cage wall three times and no spontaneous movement or righting reflex was observed for >than 1 min). To permit a quantitative assessment, the supra-spinal side-effects index was used which consisted of summing the individual scores for the five measurements at each time point, permitting a total score of 10 (5×2). Tests for the supra-spinal side effects were performed concomitantly with the antinociceptive testing.

DRUGS

Drugs used in this experiment were: dexmedetomidine (DMET; molecular weight=237, Farmos Group Ltd., Turku, Finland), clonidine-HCl (CLON; molecular weight=230.1, Boehringer Ingelheim Ltd., Ridgefield, CT), UK-14.304 (UK; molecular weight=292.1, Synaptics Pharmaceutical Inc., NY), yohimbine (YOH; molecular weight=354; Sigma Chemical Co., St. Louis, MO) and prazosin (molecular weight=419.9; Research Biochemical Inc., Natick, MA). DMET and CLON were dissolved in saline, and UK, yohimbine and prazosin were dissolved in 30% DMSO. Intraperitoneal (i.p.) injection of drugs was in a volume of 0.2 ml 100^{-1} g body weight. Control experiments used the relevant vehicle in the absence of an agonist.

EXPERIMENTAL DESIGN

Typically, rats were randomized for three sets of experiments.

(1) Agonist dose-response curves were obtained for i.t. and ICV drug administration. Dose-response curves served to define the near maximal dose for each drug for each route of administration. Each animal was used in 3–5 single experiments, animals were randomized to receive CLON, DMET or UK. Time-course curves were used to establish the time of peak agonist action for subsequent antagonist–agonist interaction studies.

(2) Antagonist dose-response studies were carried out in which a near maximally effective dose of agonist was delivered i.t. or ICV alone, or after the injection of yohimbine (0.1 mg kg^{-1}, 1.0 mg kg^{-1} i.p. or 3.0 mg kg^{-1} i.p.; 15 min before agonist injection) or prazosin (1 mg kg^{-1} i.p.; 10 min before agonist injection). To establish the time course of the maximal effect of the antagonist, a fixed dose of agonist was administered i.t. and a maximal dose of antagonist was injected at different time intervals. The measurements indicated that a maximum degree of antagonism was observed reliably within 10–15 min after injection of antagonist for all three agonists (data not shown).

(3) Agonist dose-response curves were carried out alone or in the presence of a fixed dose of yohimbine (1 mg kg^{-1} i.p.) given 10 min before administering the agonist.

Dose ratios then were calculated, being defined as the ratio of the ED_{50} of the analgesic or sedative response with the antagonist divided by the ED_{50} of the agonist without the antagonist.

STATISTICAL ANALYSIS

Data are expressed as mean (SEM). For the time course studies, latencies are indicated in seconds, each time point representing data of 4–8 animals. For further analysis the thermal latencies and the sedation index scores were converted to percentage of maximal possible effect (%MPE) according to the formula:

$$\%\ \text{MPE} = \frac{\text{response latency with drug-baseline latency} \times 100}{\text{cut-off time (20 s)- baseline latency}}$$

or,

$$\%\ \text{MPE} = \frac{\text{sedation index with drug-baseline score} \times 100}{\text{cut-off score (10)-baseline}}$$

Dose-response curves are presented as the MPE *vs* log dose. For all drugs, the dose-response analysis as described by Tallarida and Murray [26] was performed. Statistical analysis of the data was performed using the one way analysis of variance test followed by the Student-Newman-Keuls multiple comparisons test. Values of $P<0.05$ were considered statistically significant.

Results

I.T. ALPHA$_2$-ADRENERGIC AGONISTS

I.t. injection of the alpha$_2$-adrenoceptor agonists resulted in a dose-dependent increase in the thermal response latency. Maximum effects of the drugs were observed within 15–30 min (fig. 1). The ordering of the analgesic effect of i.t. drug (with ED_{50}) was DMET (1.2 nmol (0.3 μg)), UK (1.7 nmol (0.5 μg)), CLON (5.6 nmol (1.3 μg)) (fig. 2). An increase in the sedation index after i.t. administration was observed only in the DMET group (table 1). In control animals, vehicle adiministration did not produce a significant effect on analgesic or sedative variable (see below).

The administration of a competitive antagonist, yohimbine (1 mg kg^{-1} i.p.) resulted in a rightward shift of the antinociceptive effect of DMET (dose ratio=8.3), CLON (dose ratio=4.2) and UK (dose ratio=2.1) (fig. 2 and table 1).

ICV ALPHA$_2$-ADRENERGIC AGONISTS

ICV administration of the agonists produced a dose-dependent increase in thermal response latency in the DMET group (ED_{50} 12 nmol (3 μg)) and CLON group (ED_{50} 75 nmol (17.3 μg)) but not for UK (table 1). For all groups, an increase in the sedation index was also seen (DMET: ED $_{50}$=10.5 nmol (2.5 μg); CLON: ED_{50}=126 nmol (29.3 μg); UK: ED_{50}=28.7 nmol (8.4 μg)) (fig. 2). The time course for the maximal possible effect differed modestly, from 15 (CLON) to 30 min (UK) (fig.1). ICV vehicles did not show any significant analgesic or sedative effects (fig. 3).

Yohimbine (1 mg kg^{-1}, i.p.) produced a rightward shift in the analgesic effect of ICV DMET (dose ratio=1.8) CLON (dose ratio=2.6). A shift in the sedation index dose response was also observed for DMET (dose ratio=2.0), CLON (dose ratio=1.8) and UK (dose ratio=2.3) (table 1).

ANTAGONIST DOSE-RESPONSE CURVE AGAINST I.T. ALPHA$_2$-ADRENERGIC AGONISTS

The near maximal antinociceptive effect of the three i.t. alpha$_2$-adrenergic agonists was antagonized in a dose-dependent fashion by yohimbine given i.p. 15 min before agonist injection. The yohimbine ID_{50} values were found to be: 1.0 mg kg^{-1} for DMET (4.2 μmol kg^{-1}); 0.2 mg kg^{-1} (0.7 μmol kg^{-1}) for UK and 3.2 mg kg^{-1} (13.9 μmol kg^{-1}) for CLON (fig. 4).

Prazosin did not change the antinociceptive effects of the three agonists, but did affect the sedation index for CLON and UK (CLON: + 28% MPE (SEM 5%); UK + 22% MPE (SEM 3%); $P<0.05$) (fig. 5).

ANTAGONIST DOSE-RESPONSE CURVE AGAINST ICV ALPHA$_2$-ADRENERGIC AGONISTS

Yohimbine given i.p. resulted in a dose-dependent decrease in the analgesic effect of a near maximal sedative dose of ICV alpha$_2$-adrenergic agonists. A decrease in the sedation index for DMET, CLON and UK after i.p. administration of yohimbine was observed with ID_{50} values of 2.8 mg kg^{-1} (9 μmol kg^{-1}) for DMET; 5.7 mg kg^{-1} (24.7 μmol kg^{-1}) for CLON and 0.9 mg kg^{-1} (3.0 μmol kg^{-1}) for UK (see table 2 and fig. 4). Prazosin reduced the sedation index for DMET (fig. 6).

Discussion

Alpha$_2$-adrenergic agonists produce sedation and antinociception at supra-spinal and spinal sites and

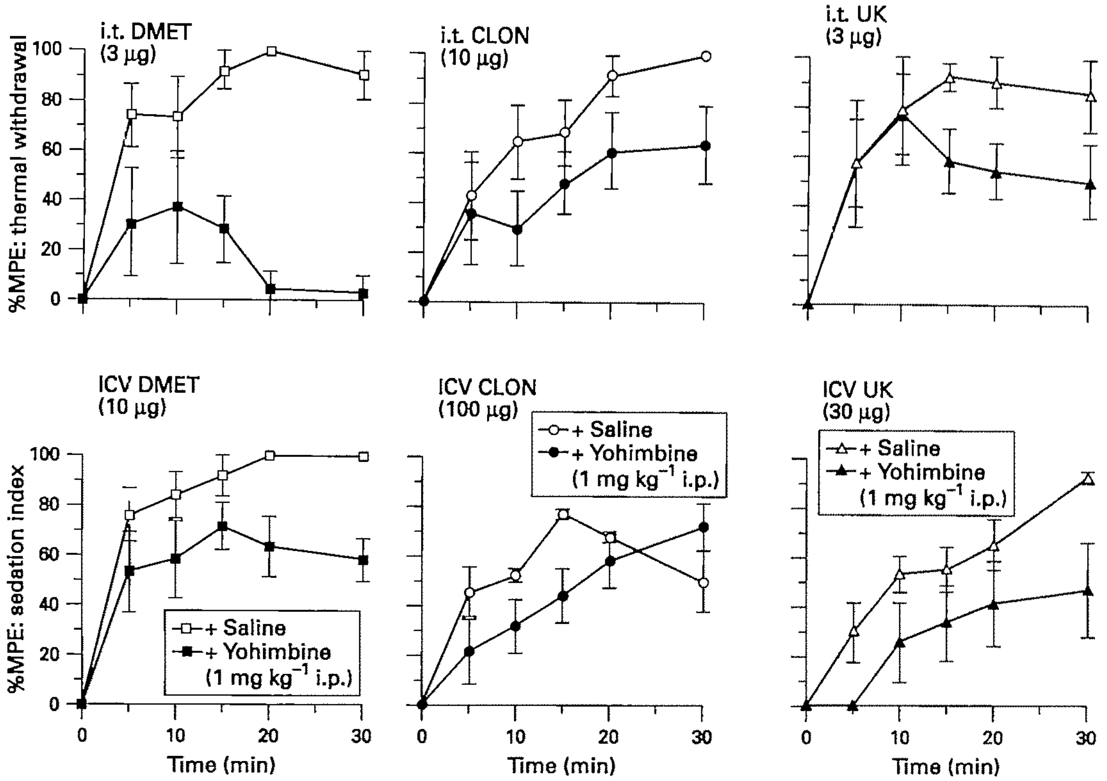

Figure 1 Time course (0–30 min) after intrathecal (i.t.) and intracerebroventricular (ICV) administration of dexmedetomidine (DMET), clonidine (CLON) and UK 14.304 (UK), maximal possible effect (MPE) of the analgesic response (thermal withdrawal) and the sedative response (sedation index) assessed in % MPE. Open symbols show the response of the drug alone; filled symbols show the response in presence after intraperitoneal (i.p.) administration of the competitive antagonist yohimbine 10 min before agonist injection. Each point presents the mean (SEM) of 5–8 animals.

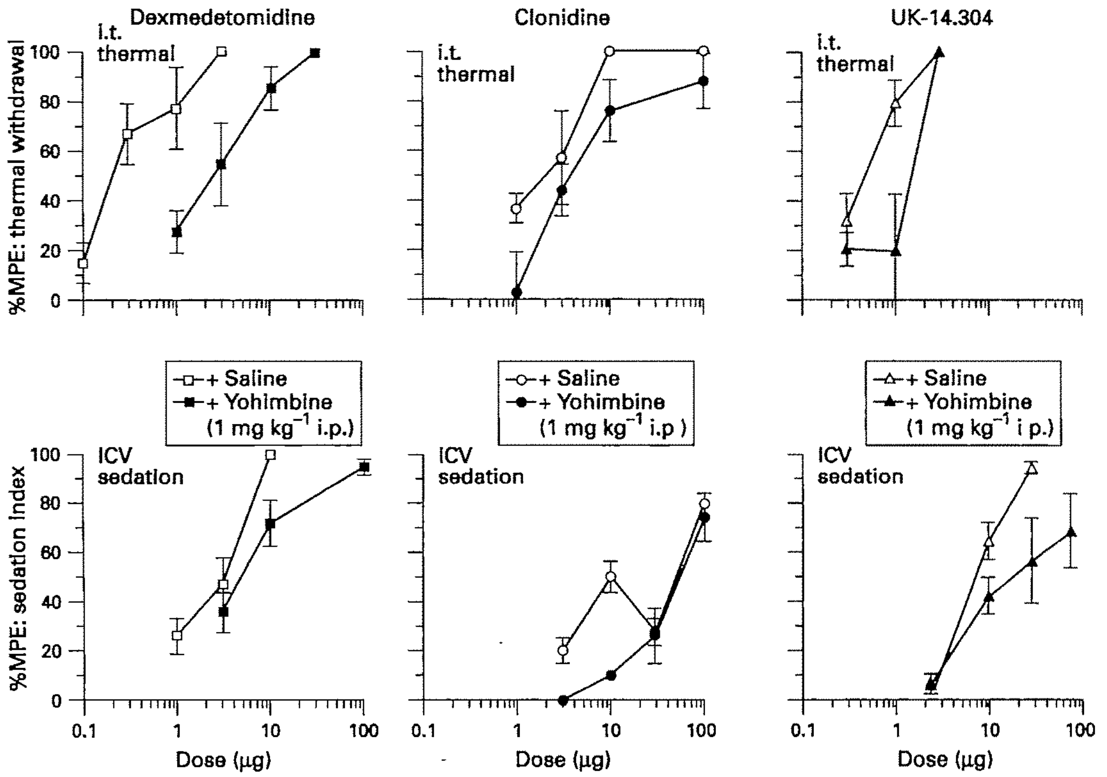

Figure 2 Dose-response curves in (0.1–100 μg) after intrathecal (i.t.) and intracerebroventricular (ICV) administration of dexmedetomidine, clonidine and UK 14.304 for the analgesic response (thermal withdrawal) and the sedative response (sedation index) assessed in %MPE. Open symbols show the response of the drug alone, filled symbols show the response after intraperitoneal (i.p.) administration of the competitive antagonist yohimbine 10 min before agonist injection. Each point presents the mean (SEM) of 5–8 animals.

Table 1 ED_{50} (95%CI) of i.t. and ICV administered alpha$_2$-agonists and thermal latency/sedation index. (bw=body weight)

	Thermal latency		
i.t.	ED_{50} (95%CI) drug without yohimbine i.p.	ED_{50} (95%CI) drug with yohimbine (1 mg kg^{-1} bw) i.p.	dose ratio (ED_{50}+/– yohimbine)
DMET	0.3 μg (0.1, 0.5)	2.5 μg (1.4), 4.6)	8.3 (4.9, 20.5)
Clonidine	1.3 μg (0.3, 6.5)	5.5 μg (2.3, 12.9)	4.2 (1.2, 16.9)
UK 14.304	0.5 μg (0.3, 0.8)	1.0 μg (0.6, 1.8)	2.1 (1.0, 4.1)
	Sedation index		
i.t.	ED_{50} (95%CI) drug without yohimbine i.p.	ED_{50} (95%CI) drug with yohimbine (1 mg kg^{-1} bw) i p.	dose ratio (ED_{50}+/– yohimbine)
DMET	1.5 μg (0.8, 2.9)	6.2 μg (4.3, 8.8)	4.1
Clonidine	>100 μg	>100 μg	no ratio
UK 14.304	>3 μg	>3 μg	no ratio
	Thermal latency		
ICV	ED_{50} (95%CI) drug without yohimbine i.p.	ED_{50} (95%CI) drug with yohimbine (1 mg kg^{-1} bw) i.p.	dose ratio (ED_{50}+/– yohimbine)
DMET	2.9 μg (2.0, 4.1)	5.2 μg (2.1, 12.9)	1.8
Clonidine	17.3 μg (6.7, 44.9)	45.5 μg (23.1, 89.7)	2.6
UK 14 304	14.6 μg (3.0, 72.2)	plateau at ED_{50}	no ratio
	Sedation index		
ICV	ED_{50} (95%CI) drug without yohimbine i.p.	ED_{50} (95%CI) drug with yohimbine (1 mg kg^{-1} bw) i.p.	dose ratio (ED_{50}+/– yohimbine)
DMET	2.5 μg (1.8, 3.6)	5.0 μg (2.3, 11.0)	2.0
Clonidine	29.3 μg (10.6, 81.3)	51.9 μg (28.7, 93.8)	1.8
UK 14.304	8.4 μg (7.0, 10.1)	19.4 μg (9.0, 41.9)	2.3

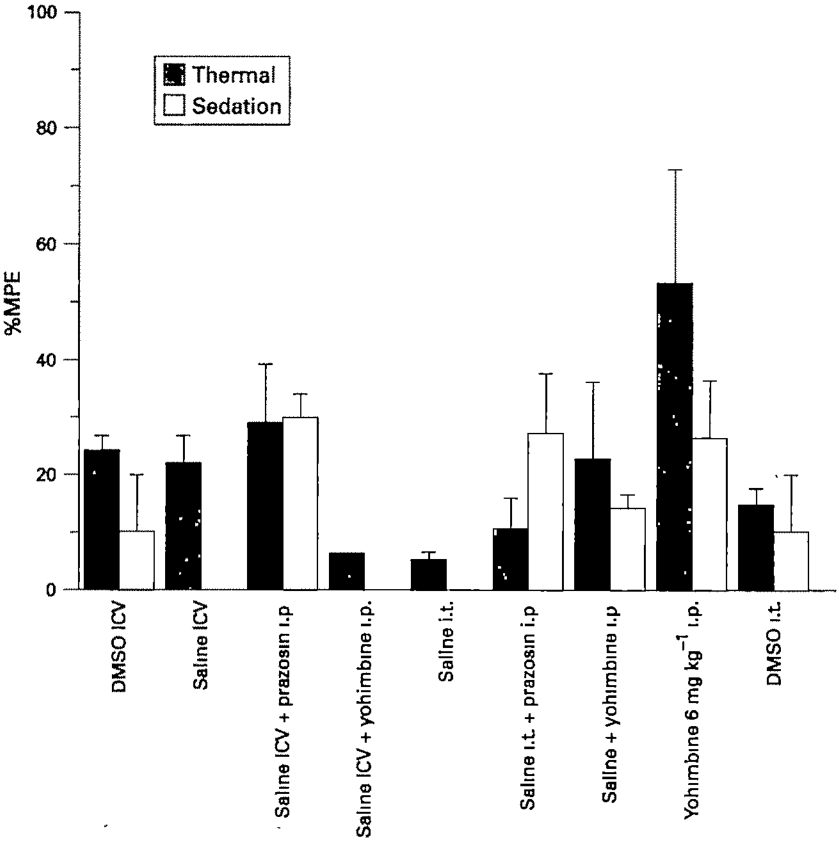

Figure 3 Data shows the effects of the vehicles DMSO and saline alone or after pretreatment with prazosin (highest dose i.p.) or yohimbine (highest dose i.p.) 10 min before i.t./ ICV injection for the analgesic response or sedative response. Each bar presents the mean (SEM) of 5 animals.

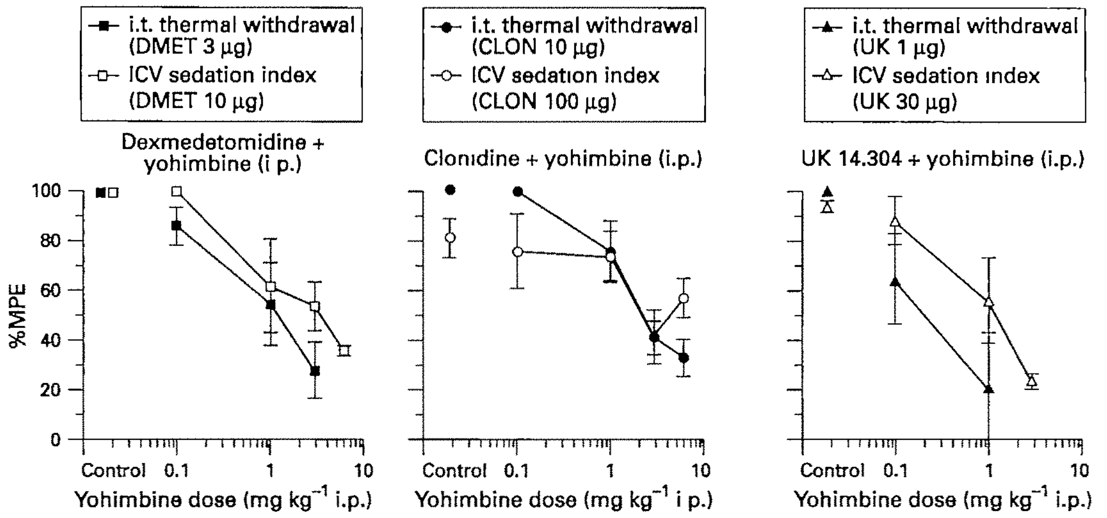

Figure 4 Dose-response curves (0.1–6 mg kg^{-1}) for the competitive antagonist yohimbine in the presence of intrathecal (i.t.) and intracerebroventricular (ICV) alpha$_2$-agonists for the analgesic response (thermal withdrawal) and the sedative response (sedation index) assessed as %MPE. Open symbols show the curve in the presence of an i.t. alpha$_2$-agonist, filled symbols show the response in the presence of an ICV alpha$_2$- agonist. Each point presents the mean (SEM) of 4–6 animals.

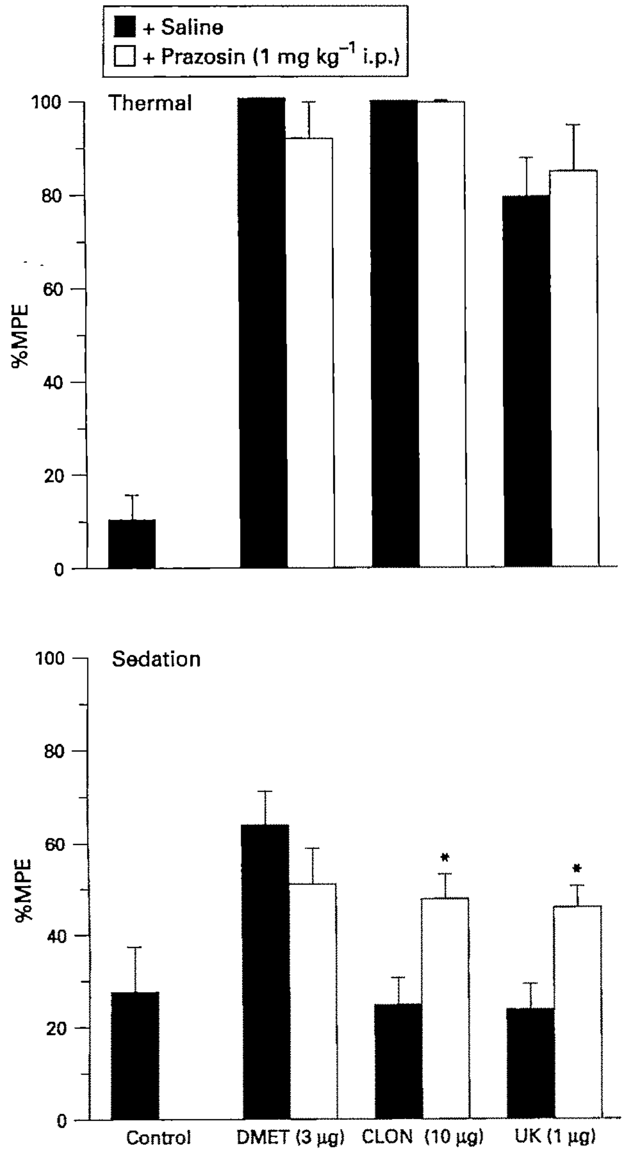

Figure 5 Data show the effects of the competitive alpha antagonist prazosin (1 mg kg^{-1} i.p.) administered 10 min before i.t. injection of different alpha$_2$-agonists or saline as control for the analgesic response or sedative response. Each bar presents the mean and (SEM) of 5 animals. * Significance of $P<0.05$.

these effects are reversed in a dose-dependent fashion by yohimbine. Previous studies have raised the possibility of different yohimbine-sensitive alpha$_2$-adrenergic receptors.[20] We sought to investigate further this interaction by systematically examining the pharmacology of three alpha$_2$-agonists in the presence of yohimbine. The purpose of our study was to compare: (a) the efficacy after i.t. and ICV delivery of several agonists in producing antinociception and sedation, respectively, and (b) to assess the ability of systemic yohimbine to reverse the i.t. (antinociception) and ICV (sedation) effects of these agonists. The efficacy of the competitive antagonist, yohimbine, is proportional to its affinity for the alpha$_2$-adrenergic receptor.[21 22 27] Thus differences in the magnitude of the dose-response shift for either the analgesic or sedative response of the three agonists in the presence of a fixed dose of the competitive antagonist, for example, yohimbine, would suggest differences of the involved alpha$_2$-adrenergic receptor sites for analgesia or sedation. Alternately, if the magnitudes of the rightward shift observed for a given i.t. or ICV agonist in producing antinociception or sedation are similar, this should provide information about the similarity of the involved alpha$_2$-adrenergic receptor sites. Dissimilar shifts would suggest an interaction with brain sites and spinal sites for which yohimbine has a distinct affinity.

I.T. ALPHA$_2$-ADRENERGIC RECEPTORS

I.t. administration of each of the three agonists resulted in dose-dependent analgesia, a finding which confirms other investigations.[20 28 29] Their relative efficacies in eliciting analgesia is similar to that described by others.[29 30] After i.t. administration, CLON and UK produced only a modest sedation score, even at the highest doses. Dexmedetomidine, however, produced dose-dependent sedation after i.t. administration. The appearance of sedation after spinal DMET is likely to be because of the greater supra-spinal redistribution secondary to the higher lipid solubility of DMET in comparison with CLON

Table 2 ID_{50} (95%CI) of i.p. administered yohimbine and thermal latency/sedation index *Plateau at ED_{50}

	Thermal latency	Sedation index
i.t		
DMET	0.98 mg (0.35, 2.73)	no ratio
Clonidine	3.18 mg (0.56, 17.98)	no ratio
UK 14.304	0.21 mg (0.03, 1.63)	no ratio
ICV		
DMET	1.57 mg (0.39, 6.21)	2.77 mg (1.19, 6.63)
Clonidine	1.97 mg (0.49, 7.83)	5.73 mg (0.01, 19.56)*
UK 14.304	no ratio	0.9 mg (0.43, 1.85)

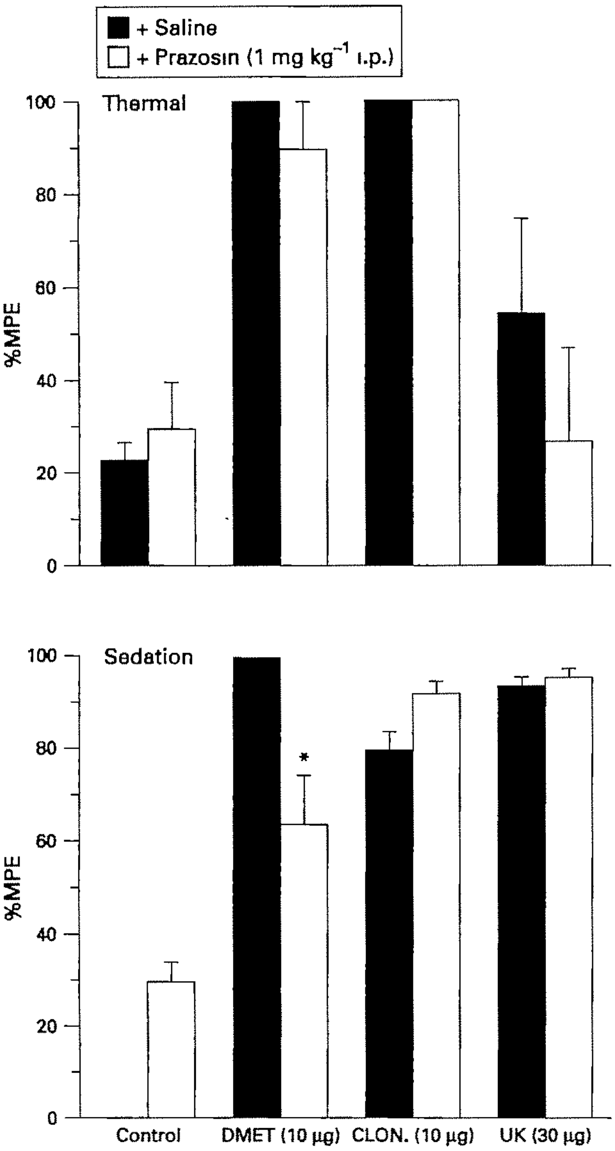

Figure 6 Data show the effects of the competitive alpha antagonist prazosin (1 mg kg^{-1} i.p.) administered 10 min before ICV injection of different alpha$_2$-agonists or saline as control. Each bar presents the mean and (SEM) of 5 animals. * Significance of $P<0.05$.

(octanol: buffer partition coefficient of 2.8 for DMET *vs* 0.8 for CLON).[31 32]

Pretreatment with yohimbine produced a rightward shift in the analgesia dose-response curve of i.t. administered alpha$_2$-agonists. The ordering of the rightward shift of DMET and CLON is comparable to the ratio found by Eisenach and colleagues.[31] The greater shift of DMET in the presence of the competitive antagonist raises several possible explanations. In binding studies,[33] the competitive antagonist yohimbine was used to reveal several populations of alpha-adrenergic receptors with differing agonist affinities. The most simplistic interpretation is that the prominent dose-response shift of DMET supports a high affinity of DMET for a yohimbine-sensitive subtype which mediates analgesia. Based on binding data reported by Uhlen and Wikberg[34] the predominant alpha$_2$-subtype in the rat spinal cord is the alpha$_2$A-adrenoceptor. This is in agreement with binding studies of alpha$_2$-adrenoceptors in the human spinal cord.[35] However, there is also well established evidence for the existence of additional subtypes (alpha$_{2D}$-adrenoceptors) in the rat.[35] Thus, while the concept of spinal non-A sites may be controversial, the functional and pharmacological differences provide support that DMET is acting at different sites within the spinal cord. Importantly, spinal UK produced only modest sedation, though this difference may be attributable to kinetics of redistribution.

ICV ALPHA$_2$-ADRENERGIC RECEPTORS

ICV administration of alpha$_2$-agonists produce a sedative response.[11 12 36] The mechanisms of this effect are not clear, but might be correlated with an inhibition of activity in the locus coeruleus of the brain stem.[11] Analgesia after ICV injection of alpha$_2$-adrenergic agents has also been reported.[37 38] The quantitative magnitude of the antagonist action, as defined by the respective dose ratios, revealed no significant differences across the three agonists. This observation suggests that the supra-spinal sedative responses were mediated through an alpha$_2$-adrenergic receptor for which yohimbine has approximately equal affinity—that is, these compounds act through a common alpha$_2$-adrenergic receptor.

After ICV injection, DMET and CLON and, to a modest degree, UK produced an increase in the thermal response latency. The analgesic action of UK was shown to be less potent than its sedative action.[37] The analgesic action of alpha$_2$-adrenergic agonists after supra-spinal administration could be caused by systemic redistribution and subsequent spinal action.[13] However, we note that the antinociceptive effects of spinal DMET were extremely sensitive to i.p. yohimbine. Thus the degree of the rightward shift in the ED_{50} for antinociception after i.t. delivery of DMET was approximately 8 *vs* 2, after ICV injection of DMET, respectively. In contrast, the similarity of the ratios for the sedative and the analgesic effects of ICV DMET argue that both effects are mediated through the same alpha$_2$-adrenergic receptor. In this regard, it is not clear whether the increase in hind paw withdrawal latency is a specific mechanism or is secondary to sedation. This alternative would explain the similarity in the ICV dose ratios for sedation and antinociception.

Prazosin, an alpha$_1$-antagonist with some alpha$_{2\text{non-A}}$-antagonist effects increased the sedative response of CLON and UK after i.t. delivery (statistically significantly), supporting the speculation that inactivation of the sedative response mediated by an alpha$_2$-adrenoreceptor is reversed through stimulation of alpha$_1$-adrenoceptors.

In conclusion, the present observations raise the possibility that the three alpha$_2$-adrenergic agonists may exert their sedative effects at a supra-spinal site for which yohimbine has a common affinity. In contrast, in the spinal cord, these three agents appear to act upon at least two sites, as defined by the differential potency of yohimbine in reversing agonist effect. These studies thus join a body of pharmacological data which suggests that there may be two spinal sites which can induce analgesia and a single supra-spinal site that results in sedation. Given the similarity of the site in brain and spinal cord as defined by the apparent potency of yohimbine, one of the spinal sites is similar to that site in brain which yields sedation. Further developments in this area may well provide a tool for which a selective analgesia may be induced by an alpha$_2$-adrenergic interaction without sedation.

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Pre-operative versus postoperative administration of morphine: impact on the neuroendocrine, behavioural, and metastatic-enhancing effects of surgery

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Summary

We have previously shown that the pre- and postoperative administration of an analgesic dose of morphine attenuated the tumour-enhancing effects of surgery. This study was undertaken to assess the relative role and exclusive importance of pre- versus postoperative morphine administration on neuroendocrine, metastatic, and behavioural outcomes of surgery in Fischer 344 rats. The natural killer (NK) sensitive mammary adenocarcinoma cell line, MADB106, was used in a lung clearance assay to assess host resistance to metastasis. Either morphine or its vehicle was administered to all rats at three times: (1) 30 min before surgery (8 mg kg^{-1}, in saline); (2) immediately after surgery in a slow release suspension (SRS, 4 mg kg^{-1}); and (3) 5 h after surgery at the time of tumour cell inoculation (2 mg kg^{-1}, in SRS). Five surgery groups underwent an experimental laparotomy with halothane anaesthesia and received either the vehicle at all three times or morphine in one of four different regimens: before surgery only, at all three times, after surgery only at times 2 and 3, and after surgery total at times 2 and 3 with the preoperative dose added at time 2. Two control groups underwent anaesthesia alone and received either morphine or the vehicle at all three times. Surgery resulted in a twofold increase in tumour cell retention, which was significantly attenuated by all four morphine treatment regimens ($P<0.05$). Furthermore, the two surgery groups that were treated with morphine preoperatively appeared to derive greater benefit; whereas the preoperatively treated groups exhibited a 65–70% attenuation of surgery-induced increases in tumour cell retention, only a 50% attenuation was evident in the two groups treated postoperatively. Surgery significantly reduced rearing behaviour and morphine reversed this effect such that most morphine-treated surgery groups exhibited similar levels of rearing behaviour as was observed in the unoperated animals throughout the 4-h postoperative observation period. Morphine treatment also significantly attenuated surgery-induced increases in plasma corticosterone concentrations assessed at 5 h after surgery. If such relationships hold in humans, these findings support the suggestion that the pre-surgical administration of morphine is key in optimizing its beneficial effects on surgery-induced increases in metastasis. (*Br. J. Anaesth.* 1998; **81**: 216–223)

Keywords: surgery; analgesics opioid, morphine; immune response, natural killer cells; rat

Both human and animal studies have shown surgery to result in a decrease in various measures of immune function, including lymphocyte mitogenic response and natural killer (NK) cell activity.[1–3] Animal studies have indicated a significant role for NK cells in controlling tumour development,[4] especially the metastatic process,[5–7] and human studies have associated low NK cell activity with increased metastatic outcomes.[8–10] These would suggest that in the clinical setting, surgery-induced suppression of NK cell activity might render the organism more susceptible to metastatic development. In support of this suggestion, multiple studies in animals have shown surgery and its consequent NK suppression to promote metastatic development.[11–13]

The role of pain in mediating these immunosuppressive and metastatic-enhancing consequences of undergoing and recovering from surgery have only recently been studied.[13–15] We have previously shown that the pre- and postoperative administration of an analgesic dose of morphine significantly attenuated the metastatic-enhancing effects of surgery while exerting no effects in the anaesthesia control groups[13 15] Furthermore, morphine treatment reversed surgery-induced decreases in exploratory behaviour,[15] suggesting its comfort-enhancing effects in these circumstances. These findings support the suggestion that providing pre- and postoperative pain-relieving medications can ameliorate some aspects of the immune suppressive consequences of undergoing and recovering from surgery, possibly by preventing pain-related neuroendocrine responses.

It is also known that morphine pretreatment can prevent the development of central sensitization from C-fibre stimulation[16]; thus, providing a rationale for the use of analgesics in conjunction with anaesthetics in individuals undergoing surgery. Indeed, the

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administration of opioids before surgery has been shown to provide improved postoperative pain outcomes in humans.[17–19] Thus, this study was undertaken in an effort to discern the relative importance of the pre- versus postoperative administration of morphine as a means to prevent the detrimental effects of surgery on host resistance against metastasis and exploratory behaviour. Additionally, corticosterone (CS), a stress hormone that is also known to be involved in modulating immune function,[20] was measured in order to begin characterizing possible mechanisms of morphine's beneficial effects in the context of surgery.

As for our previous studies, the current study used the MADB106 tumour cell line, syngeneic to the inbred Fischer 344 rat. Following i.v. injection, MADB106 cells are arrested in the lungs and surviving cells grow into lung tumour colonies. Studies have shown these two metastatic outcomes, lung tumour cell retention and the number of lung tumour colonies, to be controlled by NK cells, specifically during the first 24 h after injection.[5 7] Therefore, in addition to providing a measure of host susceptibility to metastasis, the retention and colonization of MADB106 cells in the lungs provides an indicator of NK function in the whole animal.

Materials and methods

ANIMALS

Fischer 344 male rats aged 16 to 19 weeks, age-matched within each experiment, were used in these studies. Animals were maintained in group housing on a 12-h light–dark cycle with free access to food and water except for the 8 h before surgery when only water was available. All experiments were conducted during the first half of the dark cycle. The study design was approved by the Ohio State University Institutional Laboratory Animal Care and Use Committee.

SURGERY

Surgery animals underwent an experimental laparotomy while anaesthetized with halothane (2–2.5%); animals undergoing anaesthesia without surgery were anaesthetized with halothane at the same time and in the same dose as the surgery animals. Once anaesthetized, all animals received penicillin G (25 000 units kg^{-1} i.m.), and the abdomen of the surgery animals was shaved and scrubbed with betadine solution. Surgery consisted of a 4 cm midline abdominal incision followed by the externalization of 10 cm of small intestine for a period of 4 min. The intestine was rubbed gently between two pieces of gauze in four locations during the first minute and covered with saline-soaked gauze. After returning the intestine to the abdominal cavity and irrigating with saline, the muscle and skin layers were sutured with 5–0 monofilament wire.

MORPHINE PREPARATION AND ADMINISTRATION

Morphine sulphate was administered in two different preparations. The preoperative dose, 8 mg kg^{-1}, was administered intraperitoneally (i.p.) in saline 30 min before surgery. Postoperatively, morphine was administered subcutaneously (s.c.) at the dorsal flank in a slow-release suspension (SRS), an oil emulsion comprised of mannide monooleate (Arlacel A, Sigma, St. Louis, MO), light mineral oil, and saline (6.7, 40, and 53.5% by volume, respectively).[13 15 21] The morphine concentration was adjusted such that the appropriate dose was administered in 1 ml of SRS. The postoperative dose of morphine was administered immediately after the completion of surgery just before discontinuing the halothane (4 mg kg^{-1} ml^{-1} in SRS). A second postoperative dose of morphine (2 mg kg^{-1} ml^{-1} in SRS) was administered s.c. at the contralateral flank immediately following MADB106 tumour cell injection at 5 h after surgery (Experiment 1 only). Vehicle was used for control injections.

MADB106 TUMOUR CELL MAINTENANCE AND RADIOLABELLING

MADB106 cells were maintained in 5% carbon dioxide at 37°C in monolayer culture in complete media (RPMI 1640 media (Gibco, Grand Island, NY) supplemented with 10% heat-inactivated fetal calf serum (FCS), 0.05 mg ml^{-1} streptomycin, 2 mmol litre^{-1} L-glutamine, 0.1 mmol litre^{-1} non-essential amino acid, and 1 mmol litre^{-1} sodium pyruvate). Trypsin 0.25% was used for separating the cells from the flask (Falcon 3023).

For DNA radiolabelling of MADB106 cells, 0.4 μCi$[^{125}\mathrm{I}]$iododeoxyuridine per ml media was added to the growing cell culture one day before cell harvesting. After separation from the flask, cells were washed and resuspended in phosphate buffered saline (PBS).

EXPERIMENTAL PROCEDURES

Experiment 1: The effects of the timing of morphine administration on its attenuation of surgery-induced increases in tumour cell retention

To assess the role of the pre- versus postoperative morphine treatments, animals were randomly assigned and subjected to either surgery with anaesthesia or anaesthesia alone; and either morphine or its vehicle was administered preoperatively, postoperatively, and at the time of MADB106 tumour cell injection. Table 1 summarizes the constitution of these groups and the morphine treatment regimens.

Five hours after the completion of surgery, all animals were lightly anaesthetized with halothane and injected with 4×10^5 radiolabelled MADB106 tumour cells per kg into the tail vein, followed by the third morphine/vehicle injection. Lungs were removed 14 h later and their radioactive content was measured in a gamma counter (Beckman 5500). In addition, the total radioactive content of the injectate (MAX) was measured, and percent retention was calculated using the formula: (lung radioactivity− MAX)×100.

This experiment was performed in two replicates with all groups represented in each assay. For data analysis, the percent retention for each animal was converted to a percentage of the assay mean, and these normalized scores were used for combined statistical analysis using ANOVA. For graphic illustration, normalized scores were reconverted to percent lung tumour cell retention by multiplying the normalized scores by the overall mean percentage of tumour cells retained across the two replicates.

Table 1 Morphine regimens for the seven groups comprising Experiment 1. Vehicle injections were administered at all time points in which morphine (M) is not indicated. *SRS=slow-release suspension. †The preoperative morphine dose was also administered at this time

Group	n	Morphine timing and preparation preop. 8 mg kg^{-1} in saline	 postop. 4 mg kg^{-1} in SRS*	 with tumour 2 mg kg^{-1} in SRS*
Surgery/Vehicle	15			
Surgery/Morphine	14	M	M	M
Surgery/Before-only	12	M		
Surgery/After-only	12		M	M
Surgery/After-total	16		M†	M
Anaesthesia/Vehicle	15			
Anaesthesia/Morphine	15	M	M	M

Table 2 Morphine regimens for the two assays comprising Experiment 3. Vehicle injections were administered at all time points in which morphine (M) is not indicated *SRS=slow-release suspension. †The preoperative morphine dose was also administered at this time

Group	n	Morphine timing and preparation preop. 8 mg kg^{-1} in saline	 postop. 4 mg kg^{-1} in SRS*
Assay 1			
Anaesthesia/Vehicle	13		
Surgery/Vehicle	16		
Surgery/Morphine	15	M	M
Surgery/Before-only	16	M	
Surgery/After-total	15		M†
Assay 2			
Anaesthesia/Vehicle	12		
Surgery/Vehicle	10		
Surgery/After-total	10		M†
Anaesthesia/Morphine	10	M	M
Anaesthesia/Before-only	11	M	
Anaesthesia/After-total	10		M†

Experiment 2: The effects of surgery and morphine treatment on rearing behaviour

Given our previous findings that pre- and postoperative morphine treatment prevented the activity-suppressing effects of surgery,[15] this experiment assessed the relationship between the timing of morphine administration and its ability to restore surgery-induced decreases in rearing. Animals (n=32) were randomly assigned to either the Anaesthesia/Vehicle group (n=6) or to one of five surgery groups (Surgery/Vehicle, Surgery/Morphine, Surgery/Before-only, Surgery/After-only, or Surgery/After-total (n=7, 6, 4, 3, respectively)). At the completion of surgery the animals received their postoperative morphine/vehicle treatment, and were placed in individual uncovered cages in a room illuminated with a red light. During the latter 30 min of each of the first four postoperative hours, each rear was scored by a blinded observer. One rear was scored each time the animal raised both forepaws off the cage floor. The total number of rears for each 30-min segment for each animal was analysed by repeated measures ANOVA.

Experiment 3: The effects of surgery and morphine on plasma corticosterone levels

Table 2 illustrates the group constitution and morphine regimens for the two assays that comprised this experiment. Assay 2 was undertaken to both verify findings from Assay 1 and to assess the effects of the morphine regimen on animals not experiencing pain associated with surgery.

Five hours after surgery, at the time tumour cells were injected in Experiment 1, each animal was anaesthetized with halothane within 30 s. Approximately 1 ml of blood was obtained from the heart and heparinized (20 ml^{-1}). Plasma was removed and stored at –80°C until assayed. Plasma CS concentrations were determined separately for Assays 1 and 2 using radioimmunoassay kits (ICN Biomedicals, Inc., Costa Mesa, California).

To combine results for analysis and to correct for interassay differences, the mean plasma CS concentration was calculated for the three groups common to the two assays (Anaesthesia/Vehicle, Surgery/Vehicle, and Surgery/After-total). The plasma CS concentration for each animal was converted to a percentage score of the three-group mean, and these scores were used for statistical analysis by ANOVA. For graphic illustration, percentages were reconverted to ng ml^{-1} by multiplying the percentage scores by the overall three-group mean ng ml^{-1} across the two assays.

Experiment 4: The analgesic effects of the morphine regimens

Standard hot-plate test was used to assess the duration of analgesia produced by two different morphine regimens: the before-only treatment régimen (8 mg kg^{-1} in saline, n=8), and the before-and-after treatment regimen (8 mg kg^{-1} in saline, 4 mg kg^{-1} in

SRS at 45 min, and 2 mg kg^{-1} in SRS at 4 h, n=11). Control animals received vehicle injections (n=9).

During each of the five days before the experiment, animals were habituated to handling, including transportation to and handling in the laboratory the day before the experiment. For hot-plate testing (52°C), a 45 s cut-off was used to avoid tissue damage. Baseline latency to hind-paw lick[22] was measured in all animals at time 0, and the first morphine/vehicle injection was given immediately thereafter. Hot-plate testing intervals and additional morphine dosing are indicated in figure 4.

To control for differing baseline latencies and to assess changes in hot-plate latency within animal, hot-plate latencies were converted to percent maximum possible effect (%MPE) using the formula: [latency–baseline latency)÷(cut-off–baseline latency)]×100. For both morphine groups, %MPEs were compared with the %MPE in control animals at the closest time-point tested. ANOVA was used to test the statistical significance of differences in %MPE at each time-point.

Results

EXPERIMENT 1: THE EFFECTS OF THE TIMING OF MORPHINE ADMINISTRATION ON ITS ATTENUATION OF SURGERY-INDUCED INCREASES IN TUMOUR CELL RETENTION

Surgery resulted in a twofold increase in the retention of tumour cells (Anaesthesia/Vehicle versus Surgery/Vehicle) which was significantly attenuated by all morphine treatment regimens ($F(6,92)=3.612$, $P<0.01$; protected t tests, $P<0.05$) (fig. 1). The morphine regimens that included a preoperative dose of morphine (Surgery/Before-only and Surgery/Morphine) appeared to result in a slightly larger attenuation of the observed surgery-induced increase in tumour cell retention compared with the animals receiving postoperative morphine treatment only (Surgery/After-only and Surgery/After-total). Although there were no significant differences among the morphine-treated surgery groups and the tumour cell retention observed in the preoperatively treated surgery groups was not significantly different from that of the Anaesthesia/Vehicle group, there was a significant difference between the Anaesthesia/Vehicle group and both surgery groups receiving postoperative morphine treatment only ($P<0.05$, protected t tests).

EXPERIMENT 2: THE EFFECTS OF SURGERY AND MORPHINE TREATMENT ON REARING BEHAVIOUR

Surgery resulted in a significant decrease in the incidence of rearing in the first four postoperative hours which was abolished by all morphine treatment regimens except the Surgery/After-total regimen ($F(5,26)=2.978$, $P<0.05$) (fig. 2). The animals in the Surgery/After-total group exhibited minimal activity until the third postoperative hour, when their activity level was comparable to the other morphine-treated surgery groups. Except for the Surgery/After-total group, the Surgery/Vehicle group exhibited significantly less rearing behaviour than all other morphine treated groups ($P<0.05$).

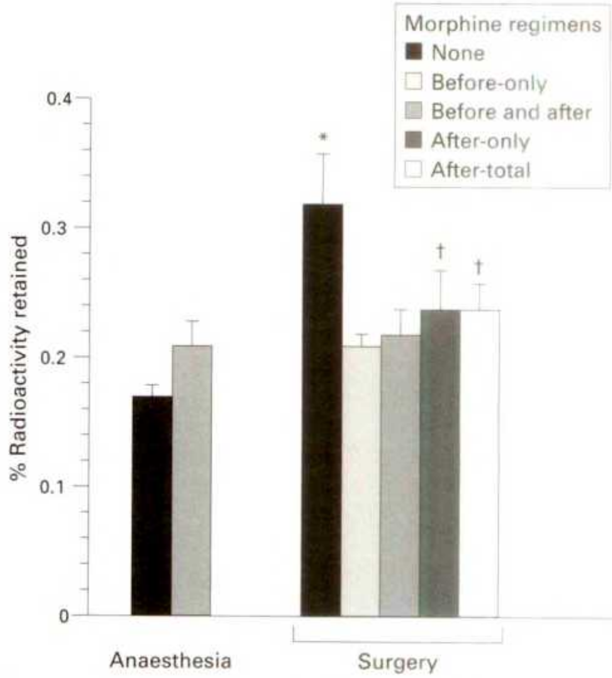

Figure 1 The effects of the timing of morphine administration on its attenuation of surgery-induced increases in tumour cell retention measured as % radioactivity retained. All animals were injected with radiolabelled MADB106 tumour cells at 5 h after the completion of surgery. Lungs were removed 14 h after tumour cell injection and their radioactive content assessed. Error bars represent SEM. * Indicates a statistically significant difference *vs* all other groups ($P<0.05$). †Indicates a statistically significant difference *vs* the Anaesthesia/Vehicle group ($P<0.05$).

EXPERIMENT 3: THE EFFECTS OF SURGERY AND MORPHINE ON PLASMA CORTICOSTERONE CONCENTRATIONS

Surgery resulted in a twofold increase in plasma CS concentrations (Surgery/Vehicle *vs* Anaesthesia/Vehicle) which was significantly reduced by all morphine treatment regimens ($F(7,130)=11.848$, $P<0.001$; $P<0.01$, protected t tests). In addition, Surgery/After-total animals exhibited significantly lower plasma CS concentrations compared with the Surgery/Morphine and Surgery/Before-only animals ($P<0.05$, protected t tests). Among the anaesthesia groups, all morphine treatment regimens resulted in a significant reduction in plasma CS compared with the Anaesthesia/Vehicle group ($P<0.05$, protected t tests). Figure 3 illustrates these findings.

EXPERIMENT 4: THE ANALGESIC EFFECTS OF THE MORPHINE TREATMENT REGIMEN

The morphine regimen for both the Before-only and Before-and-after groups resulted in a significant increase in hot-plate latencies for 60 min after the initial morphine dose, evidenced by a significant difference in the %MPE of both morphine groups compared with controls ($P<0.05$). In the Before-and-after group, no significant additional increase in hot-plate latency was provided by the SRS morphine administration (fig. 4), although the %MPE was above control levels for 3 h from the initial injection.

Discussion

The results of this study support our previous findings that the pre- and postoperative administration of

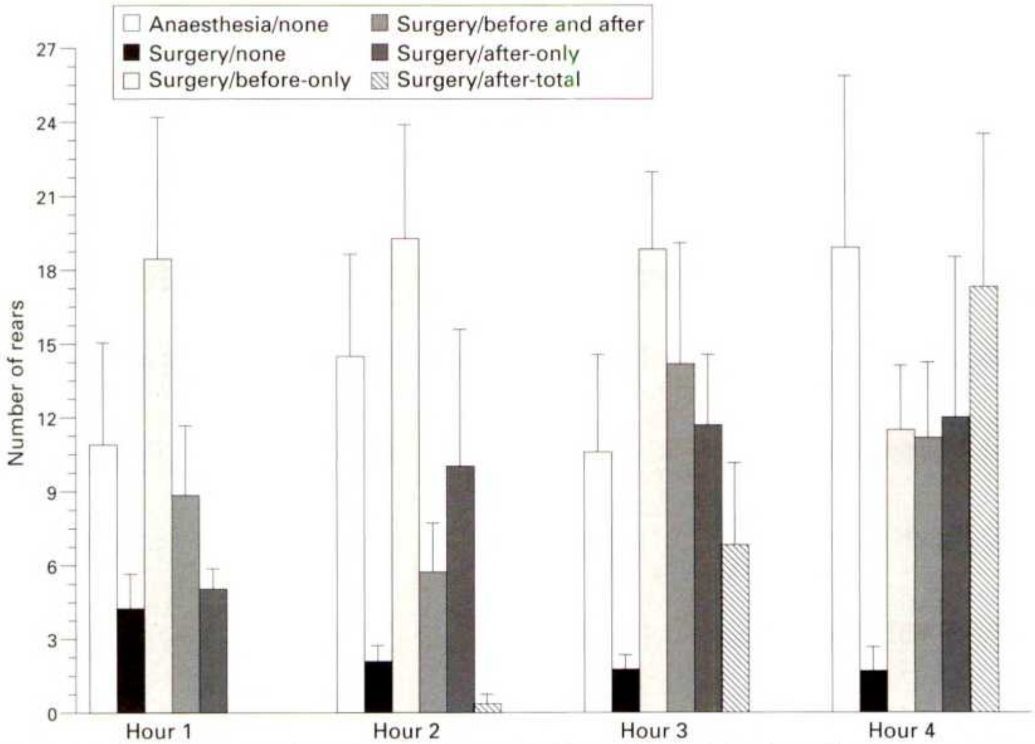

Figure 2 The effects of surgery and morphine treatment on incidence of rearing behaviours. All animals were observed for the latter 30 min of each of the first four postoperative hours. Each incidence of raising both forepaws off of the cage floor was scored as one rear. Error bars represent SEM. With the exception of the Surgery/After-total group, all other groups exhibited a significantly greater incidence of rearing compared with the Surgery/Vehicle group ($P<0.05$).

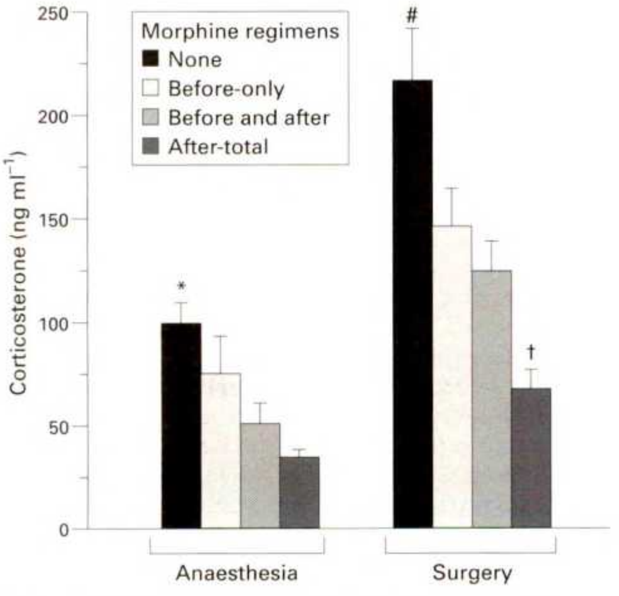

Figure 3 The effects of surgery and morphine treatment on plasma corticosterone (CS) concentrations at 5 h after surgery. Error bars represent SEM. † Indicates that the plasma CS exhibited by the Surgery/Vehicle group (filled bar) was significantly different from all other groups. * Indicates that the Anaesthesia/Vehicle group (filled bar) was statistically significantly different *vs* all other anaesthesia groups; and # indicates a statistically significant difference versus all other morphine treated surgery groups ($P<0.05$).

morphine ameliorates the metastatic-enhancing effects of surgery.[13 15] The findings show that surgery resulted in approximately a twofold increase in the lung retention of MADB106 cells, and that each of the four morphine regimens significantly attenuated this effect of surgery.

Notably, the current findings also indicate the importance of the preoperative morphine treatment in achieving these beneficial effects. Several findings suggest that, in the current experimental circumstances, the preoperative administration of morphine was the most important of the three injection times. Despite the absence of statistically significant differences in tumour cell retention among the morphine-treated surgery groups, differences are evident in the magnitude of the beneficial effects of morphine. Specifically, in comparison with the Anaesthesia/Vehicle group, surgery did not cause a significant increase in the tumour cell retention exhibited by the surgery groups treated preoperatively with morphine but it did cause a significant increase in the groups treated only postoperatively. For example, the metastatic-enhancing effects of surgery were attenuated by only 50% in both of the Surgery/After groups, in contrast with 65% in the Surgery/Morphine group, and 70% in the Surgery/Before-only group. Finally, levels of tumour cell retention in the Surgery/Before-only and Surgery/Morphine groups were equivalent; the additional 6 mg kg^{-1} of morphine administered postoperatively to the Surgery/Morphine group did not provide further protection against the tumour-enhancing effects of surgery in this paradigm. On the other hand, the two postoperative morphine regimens provided significant protection. Taken together, these findings suggest that preoperative morphine treatment is important, and in the current setting, the provision of additional doses of morphine after surgery did not further improve host resistance to surgery-induced increases in metastasis.

These findings should not be extended to the clinical setting as justification for withholding postoperative analgesic treatments for several reasons. First, postoperative morphine administration was clearly

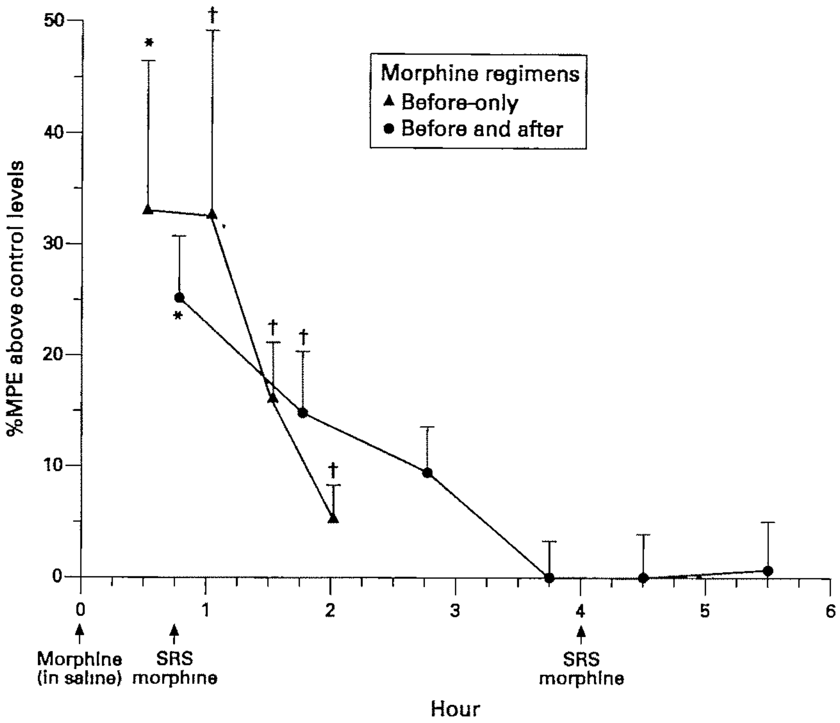

Figure 4 The effects of the before-only and before-and-after schedules of morphine administration on hot-plate analgesia (52°C) assessed as % maximum possible effect (%MPE, 45 s cut-off) above control levels. Morphine was administered after baseline hot-plate latency measurement (Time 0) to the Before-only and Before-and-after groups (mg kg^{-1} in saline), and to the Before-and-after group also at 45 m (4 mg kg^{-1} in SRS) and 4 h (2 mg kg^{-1} in SRS) later. The Before-only and Before-and-after groups were tested as indicated on the graph. The Control group was tested at time 0, 1, 2, 3, and 4.5 h. Error bars represent SEM. * Indicates a statistically significant difference *vs* the control %MPE ($P<0.05$), and † indicates $P<0.07$.

beneficial in this paradigm. Second, not only surgery-induced tissue damage but the resulting local inflammatory response can contribute to the initiation and maintenance of central sensitization; therefore, continuing postoperative analgesia would be necessary to maintain both adequate pain control and the suppression of such a hyperexcitable state.[23] This suggestion is supported by clinical findings that aggressive postoperative morphine treatment may reduce late-developing hyperalgesia.[19] Third, the use of the MADB106 tumour model might reflect some but not other aspects of host resistance to metastasis. For example, this model is very sensitive to NK activity during the first 24 h after tumour cell injection[7]; thus, resistance against the retention of MADB106 cells reflects only the earliest events involved in the establishment of metastasis, events that are NK-dependent. Finally, surgery has also been shown to suppress other immune functions such as macrophage phagocytic activity,[24 25] and macrophages have been shown to play a role in the development of a tumour colony after tumour cells have seeded in the lungs.[26 27] Therefore, the prevention of ongoing postoperative pain and stress may prove to be important in different experimental conditions.

The morphine dose used in this experimental paradigm is also important. In pilot studies to establish the optimum doses of morphine for the Surgery/Morphine regimen, we found that too little morphine exerted virtually no beneficial effects and too much resulted in tumour cell retention levels exceeding those observed in untreated surgery animals (data not shown). Others have shown that much higher doses of morphine (25–50 mg/kg^{-1}) than were used in these studies are detrimental to both immunity and tumour resistance.[28–31]

The preoperative morphine administration regimen provided significant hot-plate analgesia for 90 min ($P<0.06$), and the addition of the postoperative dose extended the analgesia by 60 min. From these data, it could be suggested that morphine exerted no measurable antinociceptive effects at the time tumour cells were injected at 5 h after surgery. However, caution is warranted in drawing inferences from the analgesic effects of morphine as evident in the hot-plate test to its pain alleviating ability in the context of undergoing and recovering from major abdominal surgery. First, the neural mechanisms by which morphine analgesia suppresses the phasic pain brought about by hot-plate testing compared with the tonic pain associated with such stimuli as surgery have been shown to differ.[32 33] Second, whereas the animals used in the metastatic, behavioural and CS experiments had undergone major surgery, those in the hot-plate study were otherwise normal. Therefore, we submit that the absence of demonstrable hot-plate analgesia at the time tumour cells were injected does not undermine the suggestion that it is the analgesic properties of morphine mediating its beneficial effects in these studies. Moreover, these findings support the suggestion that the prevention of central sensitization is a key effect of the preoperative morphine treatment.

The plasma CS results indicate that undergoing surgery activates the hypothalamic-pituitary-adrenal (HPA) axis, and this activation is reduced by morphine treatment. Given that CS has also been shown to suppress immune function,[20] reducing postoperative levels of CS may be beneficial. However, with regard to NK activity, these findings refute a causal relationship between CS levels and host resistance to metastasis. First, whereas morphine significantly

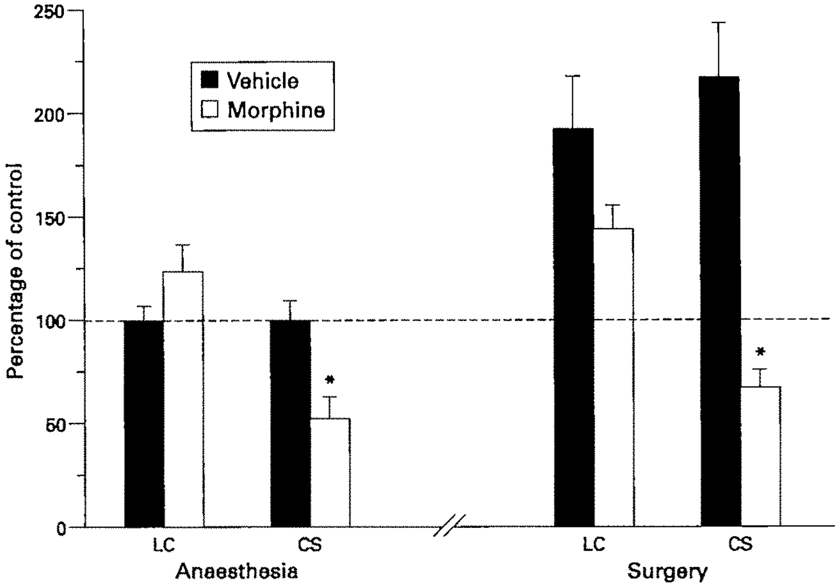

Figure 5 Graphic illustration of the interactions of morphine *vs* vehicle treatment by lung clearance (LC) *vs* corticosterone (CS) outcomes for the Anaesthesia control groups (Anaesthesia/Vehicle and Anaesthesia/Morphine) and the Surgery groups (Surgery/Vehicle and Surgery/After-total). The Anaesthesia/Vehicle group was used as the control for percent of control calculations for the LC and CS outcomes. The interactions for both the Anaesthesia controls and Surgery groups were statistically significant ($F(1,61)=9.929$, $P<0.01$ and $F(1,78)=5.868$, $P<0.05$, respectively). Error bars represent SEM. * Indicates a statistically significant difference versus the other three groups within the interaction ($P<0.05$).

reduced CS to 50% of control levels in the unoperated animals, morphine increased lung tumour cell retention in this group. Second, whereas morphine completely abrogated the surgery-induced increase in CS levels to below the baseline levels exhibited by the unoperated rats, it only partially reduced tumour cell retention in this group. Figure 5 illustrates these dissociations. This argument should be tempered, however, given that CS levels were assessed only at the time tumour cells were injected. Alternatively, pain and stress may induce their tumour-enhancing effects by activating the sympathetic nervous system.[34] In previous studies, our findings have indicated that various stress paradigms, for example, social confrontation and swim stress, suppressed NK activity and increased the lung retention of MADB106 cells via activating the sympathetic nervous system and the release of adrenal catecholamines.[35 36] In addition, this mechanism may play a role in mediating the effects of surgery.

In the behavioural study, morphine treatment restored to control levels the markedly reduced rearing behaviour observed in animals undergoing surgery without morphine treatment. Quantitatively, the morphine-treated surgery animals exhibited levels of rearing behaviour that were comparable to those exhibited by the unoperated animals. These results are consistent with our previous behavioural findings[15] and support our contention that this morphine regimen provided pain relief. The single exception is the virtual absence of rearing behaviour exhibited by the Surgery/After-total group. These animals were lying on their bellies in the sawdust for the first two postoperative hours, characteristic of animals receiving higher doses of morphine.[37] Although it did not appear to affect metastasis, these results suggest that the Surgery/After-total animals may have been overmedicated at the conclusion of surgery.

In conclusion, in the current paradigm, it appears that the preoperative dose of morphine provided the most significant contribution to improving host resistance against the observed endocrine, metastatic, and behavioural consequences of surgery. The preoperative dose alone was at least as potent as the complete regimen in affecting these measures, although its direct analgesic effects ended long before these outcomes were assessed. Nevertheless, postoperative morphine treatment alone was effective and may prove to be a more significant intervention in other circumstances. These findings support the efficacy of providing opioid medication before surgery commences as well as postoperatively. Although the current study cannot claim to prove that the observed beneficial effects of morphine are mediated by its analgesic properties, it provides ample support for this suggestion. If such findings are applicable to humans, these results provide additional evidence that the pain of undergoing and recovering from surgery poses significant risk, a risk that can be ameliorated by simply providing effective analgesia.

Acknowledgements

We wish to dedicate this work to the memory of John C. Liebeskind, our friend and mentor. We wish to acknowledge the excellent technical assistance of Singh Ahn Boun, Susan Kim, Monica Millana, and Timothy Boyer. The work was supported by NINR grant NR 03915.

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Early and late post-ischaemic recovery of contractile function is affected to different degrees by isoflurane and halothane in the anaesthetized rabbit model

S. A. ROSS, R. KATO AND P. FOËX

Summary

The protective efficacy of halogenated anaesthetics on myocardial injury has never been compared during early reperfusion and late reperfusion in an *in vivo* animal model. We compared recovery of left ventricular function under isoflurane (0.5 MAC) and halothane (0.5 MAC) anaesthesia after a brief period of regional ischaemia (15 min) in acutely instrumented rabbits. Rabbits were instrumented for the measurement of regional segment length and left ventricular pressure. Rabbits receiving isoflurane showed greater recovery of systolic shortening fraction (%SS) both during early and late reperfusion compared with halothane anaesthesia. Isoflurane protected the post-ischaemic myocardium to a greater extent than halothane anaesthesia. Early recovery of contractile function may be a predictor of contractile recovery during the later stages of reperfusion.(*Br. J. Anaesth.* 1998; **81**: 224–229).

Keywords. ischaemia; anaesthetics volatile, isoflurane; anaesthetics volatile, halothane; reperfusion; model, rabbit

"Stunning" is a phenomenon which describes the left ventricular dysfunction observed after a brief period of ischaemia.[1] This is a reversible ischaemia-reperfusion induced injury in which the time course of recovery of left ventricular function depends on the duration of the preceding ischaemia.[2] Recovery of left ventricular contractile function is biphasic in nature such that during the early stages, 2–5 min into reperfusion, there is a period where contractile function recovers to normal or supranormal levels.[3 4] This is very short-lived and, thereafter, contractile function gradually deteriorates to a minimum level from which full recovery to normal levels takes place over a longer period of time, possibly hours, days, or weeks. There has been some suggestion that this brief period represents the myocardium returning to normal function. However, the many different processes involved in ischaemia-reperfusion injury, such as free radical production, calcium overload, and impairment of myocardial perfusion, intervene and cause the subsequent deterioration of function.[5]

There have been a number of studies examining the protective effects of halogenated anaesthetics on reversible ischaemia-reperfusion injury.[6-8] The protective effects of these agents have been attributed to a number of factors; alterations in calcium fluxes,[9] free radical scavenging[10 11] and the opening of ATP sensitive K^+-channels.[12 13] Studies have shown that different anaesthetics affect these factors to differing degrees.[10] If this is the case, then it is possible that recovery during early reperfusion may differ depending on the protective potency of the anaesthetic and may be a predictor of recovery during the later stages of reperfusion.

We decided to compare the effects of two commonly used anaesthetics, halothane and isoflurane on both early recovery and later recovery to investigate if they were affected in different ways.

Materials and methods

EXPERIMENTAL PREPARATION

The study conformed to United Kingdom Animals Acts (Scientific Procedures, 1986). Nineteen New Zealand White rabbits of either sex (2.5–3.5 kg) were given xylazine (1 mg kg^{-1} i.m.) pre-medication and then anaesthetized with ketamine HCl (75 mg kg^{-1} i.m.). Adequate depth of anaesthesia was ensured before any surgical procedures by the absence of pedal and palpebral reflexes. The marginal ear vein was cannulated (20-gauge cannula) for the administration of fluids (hetastarch, 3 ml kg^{-1} h^{-1}). The central ear artery was also cannulated (18-gauge cannula) and connected to a pressure transducer (Druck Ltd, Groby, Leicester, UK) for measurement of arterial pressure during surgery. All catheters were flushed with heparinized saline (10 iu ml^{-1}) to prevent clotting during the experiment. A tracheotomy was performed (tracheal tube size 4 mm outer diameter) and the rabbits mechanically ventilated (Servo ventilator 900B, Siemens-Elema, Sweden) with 100% oxygen. The tidal volume was set at 15 ml kg^{-1} and the respiratory rate at 35 breaths min^{-1}. Ventilation was adjusted to keep the end-tidal carbon dioxide in the physiological range (4–5%). End-tidal gas concentrations were measured continuously (gas analyser M1025A, Hewlett Packard, Bracknell, UK). Anaesthesia was maintained with the appropriate anaesthetic (isoflurane 1 MAC or halothane 1 MAC[14]) depending on which group the subject was assigned to. Body temperature was recorded by the thermistor of a 7F pulmonary artery catheter (Swan-Ganz, American Edwards Laboratories, Anasco,

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Puerto Rico) inserted orally into the oesophagus and maintained between 39.0–40.5°C through a heating element incorporated into the table. Limb lead II of the electrocardiogram was continually monitored by means of s.c. needle electrodes. The heart was exposed via a left thoracotomy and suspended in a pericardial cradle. A 5–0 Dexon suture was passed around the major marginal branch of the left coronary artery approximately half way between apex and base and the suture ends threaded through a small vinyl tube to make a coronary snare. Where possible we tried to avoid snaring coronary veins but in some experiments this was not possible. The pressure in the left ventricle was measured by inserting a micromanometer-tipped 5F catheter (Millar, Houston, Texas, USA) into the apex of the heart. Two pairs of piezoelectric crystals (0.8 mm diameter, Triton, San Diego, USA) for ultrasonic measurement of segmental lengths were implanted in the subendocardium in the apical region (supplied by the snared marginal coronary artery) and the basal region (supplied by the unrestricted left circumflex coronary artery). These were implanted approximately 8 mm apart through epicardial stab wounds.

EXPERIMENTAL PROCEDURES

After surgery the anaesthetic concentration was reduced to 0.5 MAC and there was a stabilization period of 30 min after which control measurements were obtained. Regional ischaemia was then imposed for 15 min. This was followed by 120-min reperfusion. Measurements were taken after 15 min of ischaemia and then every 5 min after reperfusion for a period of 15 min with measurements being taken every 30 s during the first 5 min. Measurements were then taken at 30, 60, 90 and 120 min. To produce ischaemia the coronary snare was tightened by pulling the silk through the tubing. Ischaemia was confirmed by changes in the shape of the pressure length loop (reduction in systolic shortening, increase in post-systolic shortening and/or systolic bulging). Visually myocardial ischaemia was confirmed by the appearance of regional myocardial surface cyanosis distal to the snare, and akinesia or systolic bulging in this area. After 15 min, the snare was released and reperfusion begun for a period of 120 min. Reperfusion was confirmed by changes in the pressure length loop (increase in systolic shortening, reductions in post-systolic shortening and systolic bulging). Visually reperfusion was confirmed by the appearance of hyperaemia.

Steady state parameters were recorded for 5 s. All measurements were taken during expiratory apnoea to obtain an identical respiratory phase.

Two groups were studied; one group anaesthetized with isoflurane (group I) (n =10), and the other group anaesthetized with halothane (group H) (n =9).

DATA COLLECTION

ECG, pressures (central ear artery, left ventricular) and regional dimension signals were converted using an analogue-digital converter (AT-MIO-16, National Instruments Corporation, Austin Texas, USA), and continuously displayed on the screen of an IBM AT personal computer by means of the real-time mode of software designed in this department. Data were sampled at a frequency of 500 Hz and stored on the hard disk. Pressure-length loops were continuously displayed on an oscilloscope.

DATA ANALYSIS

Data analysis was performed on a IBM AT personal computer using the play back mode of the above mentioned software. Peak-positive and peak-negative left ventricular dP/dt were obtained by electronic differentiation of the left ventricular pressure signal. End-diastole was defined as the first upward (positive) deflection of the left ventricular dP/dt signal. End-systole was defined as occurring at peak-negative dP/dt.

Length measurements were normalized to an initial value of end-diastolic length of 10 mm at control. The following definitions were used to quantify regional wall motion: EDL=end-diastolic length; MSL=minimum length during systole; ESL= end-systolic length; L_{max} =maximum length during systole; L_{min}=minimum length during diastole. Two sets of definitions were used to describe regional wall motion.

Set 1: Systolic shortening (SS), systolic bulging (SB), and post-systolic shortening (PSS) were defined as follows:

$$SS = (EDL–ESL/(L_{max}–L_{min})\times 100$$
$$SB = (L_{max}–EDL)/(L_{max}–L_{min})\times 100$$
$$PSS = (ESL–L_{min})/(L_{max}–L_{min})\times 100$$

SS, PSS and SB were expressed as a percentage of total shortening (L_{max} –L_{min}) to show the individual contribution of each of these phases; note SS + SB + PSS = total shortening.

Set 2: Systolic shortening fraction (%SS) was defined as follows:

$$\%SS = (EDL–MSL)/EDL\times 100$$

STATISTICS

All values were expressed as mean (SD). Statistical analyses were performed using analysis of variance (ANOVA) with repeated measures. If ANOVA indicated significant differences with time during the procedure further comparisons were performed using a paired t test with Bonferroni's correction. Differences between groups were compared using an unpaired t test with Bonferroni's correction. Statistical significance was assumed at the P<0.05 level.

Results

There was no difference in general haemodynamics compared with control values or between the groups during early reperfusion therefore these data have not been included.

Table 1 shows the changes in general haemodynamics before and during ischaemia and during late reperfusion only. The only index to show any difference during control measurements was +dP/dt$_{max}$ which was significantly higher in group I. Heart rate and rate-pressure product (RPP) were significantly lower in group I compared with group H at various time points during late reperfusion.

Table 1 General haemodynamics before and during ischaemia and during late reperfusion. HR = heart rate; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; RPP = rate-pressure product; Tau = time constant of relaxation. Results are mean (±SD). † = $P<0.05$ compared with group H and * = $P<0.05$ compared with control values

	Control	Ischaemia	Reperfusion (min) 5	10	15	30	60	90	120
HR (beats min^{-1})									
I (n=10)	236 (19)	241 (19)	240 (19)	243 (22)	240 (22)	241 (22)†	236 (22)†	236 (22)	242 (25)
H (n=9)	249 (33)	264 (42)	264 (39)	270 (36)	277 (42)	276 (36)	270 (36)	266 (39)	262 (36)
LVSP (mm Hg)									
I	76 (9)	73 (9)	75 (9)	74 (9)	74 (9)	74 (9)	76 (9)	78 (13)	77 (9)
H	79 (6)	75 (9)	78 (12)	79 (12)	78 (12)	80 (9)	82 (9)	81 (9)	80 (12)
LVEDP (mm Hg)									
I	6.3 (3.8)	11.9 (6.3)	8.9 (5.0)	8.6 (4.7)	8.4 (4.7)	8.0 (3.5)	9.2 (4.7)	10.2 (6.0)	9.9 (5.7)
H	7.7 (3.0)	12.4 (4.2)	9.2 (2.4)	9.5 (2.4)	8.8 (2.4)	9.3 (3.0)	9.3 (3.3)	9.0 (3.3)	9.2 (3.3)
$+dP/dt_{max}$ (mm Hg s^{-1})									
I	2689 (499)†	2690 (686)	2639 (623)	2686 (711)	2609 (635)	2510 (531)	2575 (626)	2691 (720)	2684 (654)†
H	2210 (351)	2367 (540)	2406 (603)	2501 (711)	2440 (741)	2408 (525)	2452 (582)	2341 (633)	2208 (510)
$-dP/dt_{max}$ (mm Hg s^{-1})									
I	2444 (509)	2390 (499)	2560 (420)	2422 (446)	2311 (468)	2229 (493)	2362 (591)	2485 (638)	2445 (604)
H	2709 (411)	2530 (627)	2817 (780)	2888 (867)	2814 (918)	2852 (780)	2885 (801)	2847 (876)	2705 (840)
RPP (mm Hg min^{-1})×10^3									
I	17.9 (2.8)	17.9 (2.2)†	18.1 (2.5)†	17.9 (2.5)	17.7 (2.2)†	17.7 (2.5)†	16.5 (5.7)†	18.2 (2.8)	18.7 (2.8)
H	21.6 (4.2)	22.0 (3.0)	22.1 (4.2)	21.6 (4.2)	20.8 (3.9)	21.5 (4.2)	21.6 (3.0)	21.6 (4.2)	20.8 (3.9)
Tau (ms)									
I	15.5 (3.5)	15.5 (5.4)	16.0 (4.1)	16.8 (4.4)	17.7 (5.7)	18.8 (6.0)	18.7 (5.7)	17.9 (5.1)	17.8 (4.7)
H	16.5 (3.6)	15.8 (4.2)	15.0 (4.2)	15.1 (4.2)	14.9 (4.5)	15.0 (4.2)	15.1 (4.2)	15.6 (4.8)	16.1 (5.4)

Table 2 shows the changes in regional mechanical function before and during ischaemia and during early reperfusion. EDL showed a biphasic response during early reperfusion with a decrease from ischaemia to 150 s into reperfusion. EDL increased thereafter. %SS decreased to similar levels in groups I and H during ischaemia and increased to peak values at 90 s into reperfusion. This increase was significantly greater in group I (−1.6 (3.2)% to 20.1 (7.0)%) compared with group H (−2.7 (1.5)% to 14.8 (6.6)%). Thereafter %SS decreased in both groups with group H reaching a significantly lower value (0.7 (3.0%)) compared with group I (5.1 (5.1%)). SB and PSS showed biphasic responses with decreases during the initial stages of early reperfusion and then returning towards ischaemic values in the later stages.

Table 3 shows the changes in regional mechanical function before and during ischaemia and during late reperfusion. %SS was greater at all time points in group I except at 10 min into reperfusion. At the end of reperfusion %SS in group I had recovered to 11.8 (4.4)% whereas in group H %SS had only recovered to 7.5 (3.3)%.

Figure 1 shows the time course of changes in %SS over the entire reperfusion period, including early and late reperfusion.

Discussion

The results of our study show that in the acutely instrumented rabbit model with similar MAC concentrations of isoflurane and halothane, recovery of contractile function is greater under isoflurane anaesthesia than halothane anaesthesia. Recovery during early as well as late reperfusion was greater under isoflurane anaesthesia.

"Stunning" was first described by Braunwald and Kloner more than a decade ago.[1] The hallmark of this condition is the presence of a flow-function "mismatch" of the myocardium, with normal flow but abnormal function after a brief period of ischaemia. Since then there has been an explosion of studies examining the mechanisms involved and possible approaches to attenuate the deleterious consequences of this phenomenon. The majority of studies that examine recovery of post-ischaemic function show a simple progression from a minimum level during ischaemia to the recovery at the end of the reperfusion period. However, the recovery profile is more complex and is biphasic in nature.[3 4] There is in fact a brief period where contractile function recovers to normal or supranormal levels (fig. 1). Manche, Edmondson and Hearse[4] performed a particularly detailed study in isolated blood perfused rat hearts examining both early and late recovery after different durations of ischaemia. Their results showed that the initial recovery of function reached its maximum after 2–3 min. The results from our study are comparable with these with recovery reaching a maximum in both groups after 90 s. The early recovery observed by Manche, Edmondson and Hearse[4] could not be attributed to favourable alterations in haemodynamics. In addition, their choice of model eliminated possible neurohormonal changes or hyperaemia.

It has been known for a number of years that halogenated anaesthetics cause depression of cardiac

Table 2 Regional mechanical function before and during ischaemia and during early reperfusion. EDL = end-diastolic length; %SS = systolic shortening fraction; SS = systolic shortening; SB = systolic bulging; PSS = post-systolic shortening. Results are mean (±SD). † = $P<0.05$ compared with group H and * = $P<0.05$ compared with control values

	Control	Ischaemia	Reperfusion (s)							
			30	60	90	120	150	180	240	300
EDL (mm)										
I (n=10)	10	10.6 (0.6)	10 3 (0.3)	9.9 (0.3)	9.7 (0.3)	9.6 (0.3)	9.6 (0.3)	9.7 (0.3)	9.9 (0.3)	10.1 (0.3)
H (n=9)	10	10.4 (0.6)	10.2 (0 6)	10.0 (0.6)	9.7 (0.3)	9.6 (0.3)	8.5 (3.3)	8 6 (3.3)	9.8 (0.3)	10.0 (0.3)
%SS										
I	20.4 (6.0)	−1.6 (3.2)	7.3 (4.7)*	17.0 (5.7)†	20.1 (7.0)	18.1 (7.3)	15.3 (6.6)†*	11.8 (6.3)†*	7.1 (5.1)†*	5.1 (5.1)†*
H	20.6 (5.4)	−2.7 (1.5)	3.3 (6.9)*	8 6 (6.6)†	14.8 (6.6)	13.7 (4.8)	8.6 (4.2)*	4.8 (3.6)*	2 1 (3.3)*	0.7 (3.0)*
SS										
I	83 (19)	−20 (25)*	47 (35)†	83 (19)†	86 (16)	82 (19)	75 (25)	59 (32)	38 (25)†	27 (29)
H	87 (9)	−25 (15)*	−4 (69)	52 (36)	76 (30)	70 (27)	50 (36)	32 (33)	12 (18)*	4 (18)*
SB										
I	6 (6)	45 (16)*	22 (9)*	7 (9)	6 (6)	7 (9)	12 (13)	20 (19)	22 (16)	25 (16)*
H	4 (3)	47 (12)*	24 (24)	18 (21)	8 (9)	9 (9)	16 (12)	20 (12)	33 (18)*	31 (12)*
PSS										
I	11 (13)	74 (19)*	30 (25)†	10 (13)	7 (9)	10 (13)	12 (16)	20 (19)†	40 (13)*	47 (16)†*
H	9 (9)	78 (9)*	80 (69)	30 (30)	16 (24)	21 (24)	33 (33)	48 (24)*	55 (24)*	66 (15)*

Table 3 Regional mechanical function before and during ischaemia and during early reperfusion. EDL = end-diastolic length; %SS = systolic shortening fraction; SS = systolic shortening; SB = systolic bulging; PSS = post-systolic shortening. Results are mean (±SD). † = $P<0.05$ compared with group H and * = $P<0.05$ compared with control values

	Control	Ischaemia	Reperfusion (min)						
			5	10	15	30	60	90	120
EDL (mm)									
I (n=10)	10	10.6 (0.6)	10.1 (0.3)	10.3 (0.3)	10.3 (0.3)	10.3 (0.3)	10.3 (0.3)	10.4 (0.3)	10.3 (0 3)
H (n=9)	10	10.4 (0.6)	10.0 (0.3)	10 2 (0.3)	10.3 (0.3)	10.4 (0.3)	10.2 (0.3)	10.3 (0.3)	10.4 (0.6)
%SS									
I	20.4 (6.0)	−1.6 (3.2)*	5.1 (5.1)†*	4.2 (4.1)*	6.1 (4.1)†*	8.6 (3.2)†*	11.1 (3.2)†*	12.0 (4.1)†*	11.8 (4 4)†*
H	20.6 (5.4)	−2.7 (1.5)*	0.7 (3.0)*	1 1 (2.4)*	2.7 (2 4)*	5.2 (3.0)*	7.5 (3.6)*	7.4 (3 6)*	7.5 (3.3)*
SS									
I	84 (19)	−17 (22)*	27 (28)*	28 (28)*	50 (35)†*	70 (32)*	80 (32)*	77 (25)*	82 (28)*
H	87 (9)	−25 (15)*	4 (18)*	11 (27)*	19 (21)*	41 (24)*	53 (21)*	56 (30)	55 (27)
SB									
I	6 (6)	45 (16)*	25 (16)*	24 (13)*	20 (13)*	14 (13)	8 (13)	9 (9)	8 (9)
H	4 (3)	47 (12)*	31 (12)*	31 (12)*	21 (9)*	15 (12)	14 (6)	10 (9)	10 (9)
PSS									
I	11 (13)	74 (19)*	47 (16)†*	48 (19)*	29 (28)†	16 (25)	15 (19)	14 (16)	10 (19)†
H	9 (9)	78 (9)*	66 (15)*	58 (24)*	60 (12)*	44 (24)*	33 (18)*	34 (24)	35 (18)

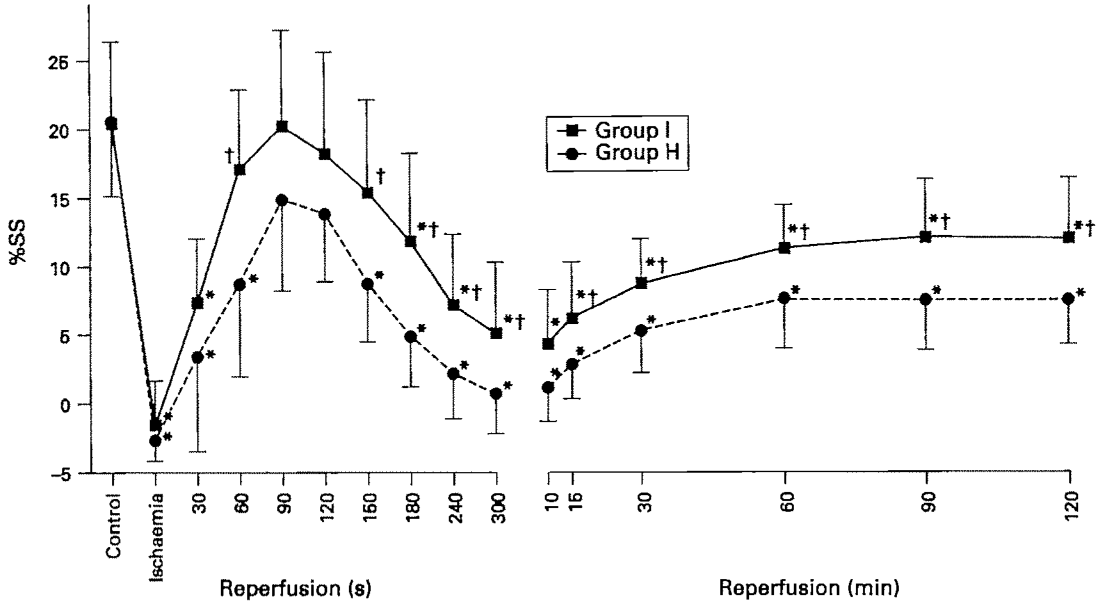

Figure 1 Change in systolic shortening (SS) fraction before and during ischaemia and during early and late reperfusion. † =P <0.05 compared with group H and * =P <0.05 compared with control values.

function[15 16] and therefore a reduction in oxygen demand of the myocardium.[17] This property of halogenated anaesthetics led researchers to consider the potential protective effects that these anaesthetics may have on the myocardium subjected to ischaemia and reperfusion. Warltier and colleagues[6] were the first group to conduct a detailed study of the recovery of myocardial function under anaesthesia with halogenated agents. They showed that recovery was greatly enhanced compared with conscious controls. Subsequent studies in both *in vivo* and *in vitro* models have shown that the protective effects of these agents cannot be solely attributed to a reduction in oxygen demand but to properties such as inhibition of calcium fluxes,[18] free radical scavenging[10 11] and KATP[12 13] channel opening activities.

In our study we found that early and late recovery of contractile function were greater under isoflurane than halothane anaesthesia. Unfortunately we could not compare these results with a conscious control. Therefore we cannot be sure that the concentration of halothane was high enough to afford protection. However, the data demonstrate that isoflurane has a greater protective effect than halothane. Studies (unpublished) examining recovery under isoflurane (1 MAC) and halothane (1 MAC) have shown even greater recovery at higher concentrations with these agents with isoflurane still providing greater protection. In the present study the rate-pressure product was higher in the halothane group and this may have accounted for the reduced recovery with this agent. However, systolic shortening during ischaemia was similar under isoflurane or halothane suggesting that the severity of the ischaemia was comparable in both groups.

Examining early recovery of contractile function we found that under isoflurane anaesthesia systolic shortening reached a higher value. One possible explanation is that isoflurane and halothane exhibit different free radical scavenging powers. At low concentrations (0.5% halothane, 0.7% isoflurane) Tanquay and colleagues[10] found in isolated hearts exposed to free radicals that isoflurane inhibited the decrease in systolic pressure to a greater extent than halothane. If isoflurane was acting as a more potent free radical scavenger at the concentrations used in the present study this may explain why contractile recovery during both early and late reperfusion was greater. A burst in the production of free radicals is known to take place within the first few minutes of reperfusion.[19] This may account for the decline in contractile function observed after the early return to normal contractile function. Early recovery under halothane did not reach the same levels as isoflurane possibly because free radicals were scavenged less and therefore affected the recovery to a greater extent.

Another explanation behind the return to normal function observed during early reperfusion is stimulation by catecholamines or calcium influx. However, Manche, Edmondson and Hearse[4] found that epinephrine and norepinephrine concentrations were constant as long as adequate anaesthesia was maintained. A transient increase in calcium influx would also stimulate hyperactivity. If this was the case one may expect contractility to reach supranormal levels. We did not find this; recovery under isoflurane reached 98% of control values. The myocardial cell also expresses transporters (Na^+-Ca^{2+} exchange)[20] which can rapidly normalize calcium levels.

We believe that this is the first study to show that early recovery as well as late recovery can be affected to different degrees by different anaesthetics. As contractile recovery during this early phase followed the same pattern as during the later stages (%SS in group I > group H) it would seem reasonable to assume that the greater recovery during early reperfusion implies a greater degree of protection and therefore greater recovery during the later stages of reperfusion.

An effect of an anaesthetic on this hypercontractile phase has been reported previously. Wouters and colleagues[21] observed that during reperfusion of the myocardium the hypercontractile phase was greater in isoflurane anaesthetized dogs than conscious dogs. The authors could not provide an explanation for this effect but eliminated drug-specific effects on coronary and systemic vessels. Again this would suggest that isoflurane protects the myocardium during the early stages of reperfusion.

We have only studied the effects of two anaesthetics at one concentration in this study. Further studies are in progress using other anaesthetics at different concentrations to determine if our theory that early recovery may be a predictor of late recovery after reversible ischaemia-reperfusion injury holds true.

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REVIEW ARTICLE

Thoracic paravertebral block

J. RICHARDSON AND P. A. LÖNNQVIST

Paravertebral nerve block produces ipsilateral analgesia through injection of local anaesthetic alongside the vertebral column. It is advocated predominantly for unilateral surgery, for example, thoracotomy, chest wall trauma, breast surgery, cholecystectomy, herniorrhaphy or renal surgery, although it can be used as a bilateral technique. In chronic pain, it is used for the treatment of benign or malignant neuralgia. There is confusion over the indications for this block and it is apparent that much ignorance surrounds this subject. Its place alongside extradural, intercostal and interpleural analgesia requires elucidation. The aim of this review is to describe the anatomy, techniques, analgesia, side effects and complications of paravertebral nerve blocks so that a more considered use of this form of analgesia can be undertaken.

History of paravertebral blocks

A requirement for analgesia and abdominal muscle relaxation during surgery led Hugo Sellheim of Leipzig (1871–1936) in 1905 to perform the first paravertebral block.[7 51] His aim was to find a replacement technique for spinal anaesthesia, devoid of its feared hazards of cardiovascular and respiratory collapse. A surgical resident in Leipzig, Arthur Läwen (1876–1958), made a special study of this new technique. Through the painstaking injection of small quantities of procaine at the emergence of each spinal nerve in many hundreds of patients with abdominal pain who subsequently underwent laparotomy or postmortem examination, Läwen (with others), mapped out the segmental innervation of the intra-abdominal organs. He then developed this knowledge into a powerful diagnostic tool.[41] Not only could a few millilitres of local anaesthetic at the appropriate spinal levels indicate the organ from which the abdominal pain was arising, but it also aided palpation through relaxation of abdominal muscle spasm. Its particular use was in the differentiation of ureteric from gallbladder colic, but it was also indicated in the differential diagnosis of stomach compared with pancreatic, duodenal or gallbladder pain.[7 51] Injections were investigated at all vertebral levels, from the cervical region where they are better known as cervical plexus and stellate ganglion blocks, to the sacral region where in effect they become caudal extradural blocks.

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Keywords: anaesthetic techniques, regional, paravertebral; anaesthetics, local, bupivacaine; pain, postoperative

Although originally the main therapeutic indication for paravertebral nerve blocks was the relief of surgical pain, in the early years of this century its applications flourished. These grew to include the alleviation of angina pectoris, the intractable pain of malignancy, pain from fractured neck of femur, and ischaemic limb pain including causalgia and post-traumatic sympathetic dystrophies. It was also used for treating supraventricular tachycardias, bronchial asthma, aiding the passage of renal and gallbladder stones, and the management of pain from herpes zoster.[51]

Its popularity reached a peak in the 1920s and 1930s following which, during the 1950s and 1960s, publications about this technique almost completely disappeared. In the late 1970s, at the same time as negative views were being expressed in textbooks, publications slowly started to reappear. The past decade has seen an upturn of interest and study.

Anatomy and mechanism of analgesia (figs. 1 and 2)

The paravertebral space is a wedge-shaped area sandwiched between the heads and necks of the ribs.[50] The posterior boundary is the superior costotransverse ligament and laterally, the posterior intercostal membrane. Anteriorly is the parietal pleura, and the base of the triangle (medially) is the postero-lateral aspect of the vertebra, the intervertebral disc and the intervertebral foramen.[50] The nervous contents of each paravertebral space are: the spinal (intercostal) nerve; its dorsal ramus; the rami communicantes; and, anteriorly, the sympathetic chain. The spinal nerve as it emerges from the intervertebral foramen is devoid of a fascial sheath and is often broken up into small nerve rootlets which are therefore easily penetrated by local anaesthetic.[62] This area also contains some loose extrapleural fascia. There is no lateral limit; it is contiguous with the tissue plane between the intercostal muscles, that is, the intercostal space. The distribution of solutions injected into the paravertebral space have been observed in cadaver studies with resin[17] or coloured dye,[47 61 62] radiologically with contrast media[18 20 24 29 42 46 55 66] and clinically with instillation of methylene blue at thoracotomy.[59 83] Solutions can: (1)

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remain localized; (2) spread superiorly and inferiorly across the heads and necks of the ribs to the spaces above and below; (3) pass medially through an intervertebral foramen; (4) spread laterally in the intercostal plane.

Gross anterior spread is not possible unless the parietal pleura has been traumatized.

There is some disagreement over the inferior limit of spread; the origin of the psoas muscle probably preventing any spread below T12.[47] A somatic block of lumbar dermatomes has been seen to accompany a thoracic paravertebral block, although this may have occurred either by spread anteriorly into the transverse fascia of the abdominal cavity through the medial and lateral arcuate ligaments to effect a lumbar plexus block,[90] or through extradural spread.

The mechanism of action of paravertebral analgesia is by direct penetration of local anaesthetic into the intercostal nerve, including its dorsal ramus, the rami communicantes and the sympathetic chain.[24 101] Mass movement of drug across further tissue planes, as required for example for intrapleural block, is unnecessary for analgesia as the nervous structures are adjacent to the needle point or within the same tissue plane.

An accompaniment of the somatic block is a unilateral sympathetic block. This is because of penetration by local anaesthetic into the sympathetic chain and the slender rami communicantes.[24 101] In a study of chronic pain patients undergoing paravertebral blocks with 0.5% bupivacaine 15 ml, a mean somatic block of 5 dermatomes was accompanied by a mean sympathetic block of 8 dermatomes, as evidenced by ipsilateral skin warming demonstrated by thermography.[14]

Indications

Thoracic paravertebral blocks are particularly advocated for unilateral surgical procedures, for example, thoracotomy,[3 13 53 60 72 75 85 87] breast surgery,[30] cholecystectomy[5 27 42 46 61] and renal or ureteric surgery.[42 43 46 49] It can also provide analgesia for rib trauma[23 28 29 55 103] and herniorrhaphy.[19 89 90] It has been used as a bilateral technique in thoracic surgery[96] and major abdominal vascular surgery.[82] In chronic pain management, it is used for the treatment of benign or malignant neuralgia,[7 10 14 23 38 40 66 94] in the management of complex regional pain syndromes with a sympathetic component, and in the therapeutic control of hyperhydrosis.

Techniques

The standard technique of space location is by loss of resistance to air or saline.[23 71] The patient can be in the prone, lateral (usually with the side to be blocked uppermost) or sitting position. Two or three centimetres lateral to the spinous process, a short bevelled 8- or 10-cm spinal needle, or a Tuohy needle if a catheter is required, is advanced perpendicular to all skin planes. At approximately 2 to 5 cm in an adult, the transverse process should be contacted. Upon bony contact, the needle is re-angled superiorly and advanced 1 or 1.5 cm over the top of the process until loss of resistance to air or saline is appreciated. A "click" may be appreciated as the superior costotransverse ligament is penetrated. The depth from the skin is variable but in the thoracic region the paravertebral space is usually 4–6 cm. Paraesthesiae may be experienced by an awake patient in the distribution of the anterior ramus, but if they occur in the distribution of the posterior ramus (that is, over the skin of the back) it does not necessarily mean that the needle point is correctly positioned, as posterior branches of the spinal nerve may have been contacted in spinal muscle.

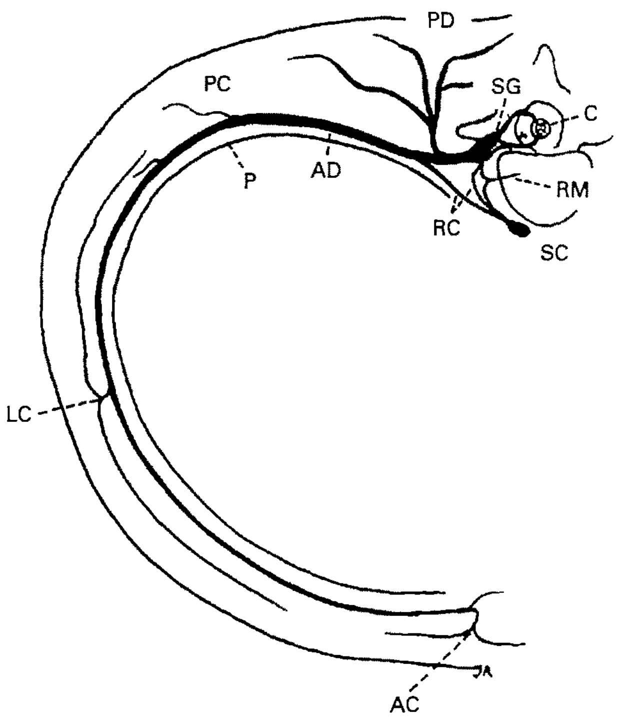

Figure 1 Schematic thoracic spinal nerve. AD=anterior division, PD=posterior division, C=spinal cord, SG=spinal ganglion, RM=recurrent meningeal, SC=sympathetic chain, RC=rami communicantes, PC=posterior cutaneous, LC=lateral cutaneous AC=anterior cutaneous, P=pleura.

It should be noted that compared with extradural space location where a very resistant ligamentum flavum is traversed, followed by almost free injection, thoracic paravertebral space location by this method is somewhat indefinite. False positive losses of resistance may occur when the needle tip is radiologically embedded in muscle. With advancement, penetration of the superior costo-transverse ligament may not be appreciated, following which false negative losses of resistance may occur as paravertebral areolar tissue provides more resistance to injection of air or saline than extradural fat. There may therefore be encouragement for further needle advancement and hence pleural penetration. In patients who are either tender, obese or very muscular, prior location of the aiming point of the transverse process may be impossible. Scar tissue in the paravertebral space, for example, in previous thoracotomy patients, can interfere with the appreciation of a loss of resistance.

There are two supplementary ways of improving the reliability of space location. X-Ray screening with contrast injection is helpful if the facilities are readily available. The appearances have been described as "linear streaming" where dye is seen, over the course of a few seconds, to spread superiorly and inferiorly over the heads and necks of the ribs, alongside the vertebral column. Otherwise a "cloud-like" appearance may be seen; here, contrast medium is more localized and spreads along one or two intercostal

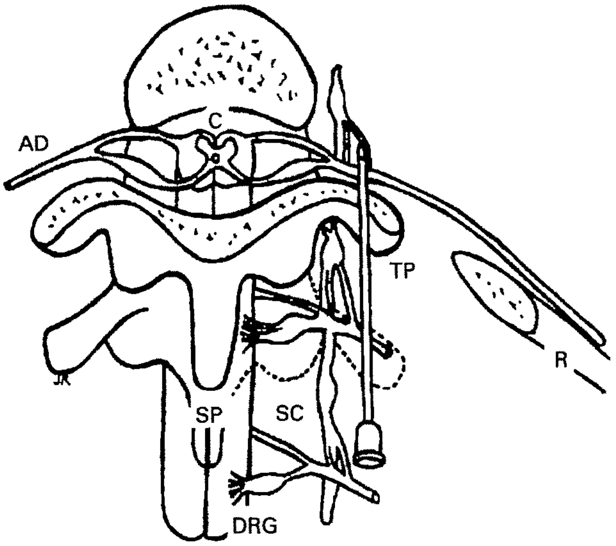

Figure 2 Optimal needle position in relation to the transverse process of the vertebra (TP) and the nervous structures of the thoracic paravertebral space (Adapted from Mandl[51]) R=rib, AD=anterior division, SP=spinous process, SC=sympathetic chain, DRG=dorsal root (spinal) ganglion, C=spinal cord.

spaces.[46] Either appearance leads to an adequate block.[46]

Pressure monitoring can be used as an alternative or supplementary technique.[70] A transducer is connected to the end of a Tuohy needle via a three-way tap and a pressure waveform is displayed during needle advancement. In muscle, the pressure is greater on inspiration than expiration, either because the posterior spinal muscles are active during inspiration, or else that they are compressed by the expansion of the chest cage against the elastic confines of the skin. With advancement, there is a sudden lowering and inversion of pressures when the paravertebral space is reached, because of the transmission of subatmospheric intrapleural pressure on inspiration. Inadvertent puncture of the pleura is readily appreciated as both inspiratory and expiratory pressures become subatmospheric on quiet respiration.[35] This objective technique improves sensitivity and specificity.[70] The lateral distance from the spinous process to the paravertebral space and the depth of the skin to the paravertebral space have been found to correlate well with age, height, weight and body surface area in children and adolescents.[45]

Catheter techniques are straightforward but it should be noted that some manipulation of needle angulation may be necessary and greater force in feeding the catheter is needed compared with extradural catheterization. We do not recommend the insertion of more that 4 cm of catheter in an adult or 2–3 cm in children, as inadvertent lateral projection into an intercostal space may encourage just one dermatome analgesia (see below) (fig.3).

Sabanathan described a method of catheterization for use in chest surgery.[83] Before thoracotomy closure, the parietal pleura is stripped up to the vertebral bodies and a blunt dissection of the extrapleural fascia, two dermatomes above and two below the incision, is carried out. An externally introduced Tuohy needle is advanced into the paravertebral space and an extradural-type catheter is advanced under direct vision into position alongside the vertebral column. The parietal pleura is then replaced and held in position by two sutures. Through the combination of direct vision and the preparation of a pocket for local anaesthetic, these modifications make for a very highly reliable technique, even in infants of a median age of 1.5 weeks (fig.4).[3 15 34 86 87]

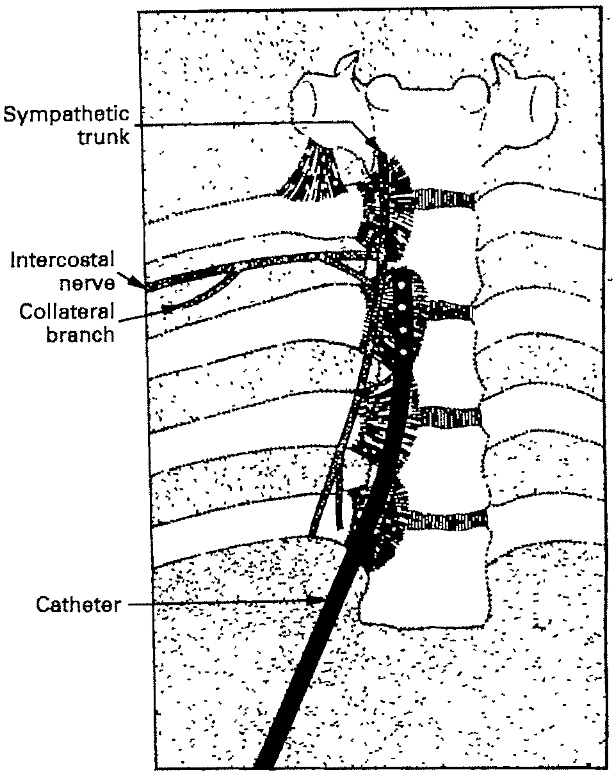

Figure 3 Optimal position of a paravertebral catheter.

In thoracic surgery, these methods can be combined.[86 87] A percutaneous bolus of bupivacaine given by the anaesthetist through the loss of resistance or pressure monitoring technique, provides analgesia for the intraoperative period. A catheter can be placed at the same time and methylene blue can be injected before chest closure to confirm or refute its successful position. If spread of dye is optimal, that is, over the heads and necks of the ribs above and below the injection for at least 4 dermatomes, it is left *in situ*. If spread is suboptimal it can be replaced by the surgeon before chest closure. The positioning of a catheter under direct vision has been described during thoracoscopy.[96]

Nursing surveillance

No additional nursing skills or observations are necessary other than those required for the care of postoperative patients.[73] An aseptic technique is required in changing an infusion syringe and an in-line bacterial filter is advocated.

Drugs used

Drugs used include bupivacaine, bupivacaine with epinephrine, bupivacaine with corticosteroid (personal experience) and lidocaine with epinephrine. The dose of local anaesthetic required involves a consideration of the number of dermatomes which it is

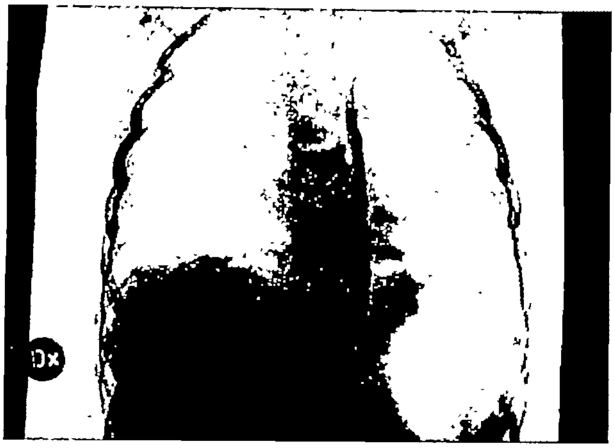

Figure 4 Radiographic appearances after contrast medium infusion through a correctly placed paravertebral catheter. Contrast is confined to, but well distributed within, the adjacent paravertebral spaces showing a longitudinal streaming effect.

desired to block. No reliable formula has as yet been developed, but it can be assumed in an adult that a volume of 15 ml will spread over and block at least 3 dermatomes,[5,14,20,23,28,29,66,70,71,78,83,87,96] and in children a bolus dose of 0.5 ml kg^{-1} will reliably cover at least 4 dermatomes.[46]

In adult thoracotomy pain management, we use bupivacaine with a concentration ranging from 0.25 to 0.5%, starting with a bolus dose of 15–20 ml, at least 10 min before skin incision. A further bolus of 0.5% bupivacaine 10 ml is given during chest closure and this is followed by an infusion of 0.5% bupivacaine at a rate of 0.1 ml kg^{-1} h^{-1} for 2 days, after which the concentration is lowered to 0.25% for a further 3 days.[86] Other authors agree that continuous infusion provides better analgesia than intermittent bolus doses.[12]

Pharmacokinetics

The two local anaesthetic agents which have been studied are bupivacaine and lidocaine, both with and without epinephrine. The mean (SEM) maximum plasma concentration (Cpmax) obtained with a bolus of 0.5% bupivacaine 20 ml is 1.45 (0.32) µg ml^{-1} with a median (range) time to Cpmax (tCp max) of 25 (10–60) min. After the initial peak with the bolus injection, there is a gradual increase to a mean (SEM) peak concentration of 4.92 (0.7) µg ml^{-1} at 48 h (5–96).[4] There were no symptoms or signs of toxicity in this study. Similar levels were found in a previous study using these methods, but additionally it was found that of the total bupivacaine levels, there was a higher concentration of the *S*-enantiomer, of which there is evidence for less toxicity compared with the *R*-enantiomer.[16]

Patients with a median age range of 5.3 weeks given a bolus followed by infusion of 0.25% bupivacaine for post-thoracotomy pain relief had satisfactory peak loading dose and infusion levels.[34] In a subsequent study of even smaller infants, given 0.125% bupivacaine, satisfactory levels were again shown.[15]

The preliminary results of a comparison of 0.25% bupivacaine compared with 0.25% bupivacaine with epinephrine 20 ml 1:200 000 given as a bolus dose of 1 mg kg^{-1} to thoracotomy patients, was reported by Snowden and colleagues.[95] The Cpmax ranged from 0.48–1.08 µg ml^{-1} (median 0.705) in the bupivacaine with epinephrine group, compared with 0.27–2.39 µg ml^{-1} (median 0.918) in the bupivacaine group. Although this difference was not statistically significant, the lowering of maximal plasma bupivacaine concentrations with epinephrine containing solutions has also been shown with intercostal nerve blocks[32] and would seem logical. The median (range) tCp max was 5 min (5–20) for both groups.

We have measured plasma concentrations of lidocaine in children undergoing renal surgery.[43] Patients were given a bolus of lidocaine 0.5 ml kg^{-1} (10 mg ml^{-1}) with epinephrine (5 µg ml^{-1}), followed by an infusion of 0.25 ml kg^{-1} h^{-1} of the same solution which was started 2 h after the initial bolus injection and continued for 10 h. Peak concentrations ranged between 1.7 and 3.0 µg ml^{-1} after the bolus with a tCp max of 15–30 min. Steady state levels of lidocaine were reached 8–10 h after the start of the infusion and ranged from 2.1–3.2 µg ml^{-1}. These moderate levels were not associated with symptoms or signs of toxicity. We have been unable to find any clinical reports of severe central nervous system or cardiovascular system toxicity either because of excessive systemic local anaesthetic levels or profound sympathetic block.

Efficacy

Particularly when used as a method of providing unilateral analgesia for unilateral surgery, paravertebral blocks can provide high quality pain relief, as shown by low pain scores and an opioid sparing effect.[3,11,60,72,75,83,85] Sufficient analgesia in some situations, particularly breast surgery, has obviated the need for general anaesthesia.[30,78]

Pre-emptive paravertebral blocks before thoracotomy combined with continuous postoperative paravertebral blocks as part of a balanced perioperative technique has led to pain scores of less than 0.5 cm on a scale of 0–10 cm, with almost complete preservation of pulmonary function and with stress inhibition (as shown by glucose and cortisol estimation).[75,80] Stress inhibition has also been shown after cholecystectomy,[27] effects which cannot be demonstrated for these types of surgery with more central forms of afferent block.[37,79,92] Post-thoracotomy pulmonary function has been studied and found to be better preserved with paravertebral blocks than with systemic opioids,[3,83,85] intrapleural bupivacaine[76] or extradural bupivacaine.[79] The ability to perform pulmonary function tests in the presence of a large chest wound is an objective measure of pain control. Postoperative pulmonary complications and hospital stays are reduced,[3,75,83,86–88] as is the generation of chronic pain (post-thoracotomy neuralgia).[77]

Comparative studies

EXTRADURAL ANALGESIA

In comparing the analgesia which can be obtained with extradural compared with paravertebral blocks, Matthews and Govenden found that pain scores at rest after thoracotomy were similar with both techniques but the side effects of postural hypotension and urinary retention were significant problems only with extradural analgesia.[55] We have compared extradural morphine and paravertebral bupivacaine after thoracotomy and found similar results; pain relief was similar but troublesome side effects, especially urinary retention, accompanied extradural analgesia.[72] We have also studied extradural bupivacaine compared with paravertebral bupivacaine for perioperative thoracotomy pain management.[80] Pain relief was the same, but opioid requirements were less in the paravertebral group, with consequently less opioid related side effects. Pulmonary function was significantly better in the paravertebral group and stress responses, as measured by cortisol and glucose assay, were suppressed in the paravertebral group, but not in the extradural group.

In a retrospective comparison of the analgesia obtained by extradural blocks compared with paravertebral blocks in children undergoing renal surgery, we found the need for supplemental morphine administration was significantly lower in the paravertebral group and the number of patients requiring no supplemental morphine was significantly higher in the paravertebral group.[49]

In contrast with these studies that have favoured paravertebral techniques, must be set two other investigations that have shown equivocal results. Pertunen and colleagues carried out a comparison of extradural, paravertebral and intercostal blocks for post-thoracotomy pain. Similar levels of pain, opioid requirements, pulmonary function and adverse effects were found in all groups.[64] Bigler and colleagues compared extradural bupivacaine and morphine with paravertebral bupivacaine in post-cholecystectomy patients. Both groups were given boluses preoperatively followed by the same drugs by infusion postoperatively.[5] Pain scores were significantly better in the extradural group compared with the paravertebral group. There was no difference in their effects on pulmonary function.

In conclusion, both techniques lead to high quality pain relief which can be associated with good preservation of postoperative pulmonary function. Stress modification has been shown with paravertebral blocks. The choice of an optimal regional technique probably comes down to other factors such as contraindications, side effects and possible complications (see below).

INTERCOSTAL BLOCKS

These blocks are done by injecting local anaesthetic into the same tissue plane as for a paravertebral injection, but usually approximately 8 cm from the midline. This single difference makes for very dissimilar effects:

(1) Multiple level spread is discouraged. Johansson, carefully studying healthy volunteers found that 0.5% bupivacaine 20 ml deposited 8 cm from the midline (that is, intercostally) blocked just one level.[31]

(2) Catheter techniques are cumbersome and unreliable: the use of up to 4 catheters at any one time has been described.[63] Repeated intercostal nerve blocks are therefore required which are painful, time consuming and compound the risks of a pneumothorax.[6 39]

(3) In this relatively distal position along the length of the intercostal nerve, it could not be expected that the sympathetic chain, the rami communicantes or the dorsal ramus are reliably blocked. Studies on the use of intercostal nerve blocks for pain after postero-lateral thoracotomy have reported unrelieved back pain (caused by damaged costotransverse and costovertebral structures), or unrelieved shoulder pain probably because of failure to block these structures.[104]

(4) The complications of pleural or pulmonary damage would be expected to be greater than with paravertebral blocks, because of the relative shallowness of the intercostal space distally compared with its triangular shape alongside the vertebral column (paravertebrally). Comparisons are difficult but the incidence of pneumothorax after intercostal block has been reported to range from 0.073% to 19%,[58] compared with approximately 0.5% with paravertebral blockade.[48 71]

Having made these observations, we are aware of only one direct comparison, that of Pertunen and colleagues.[64] They compared extradural, paravertebral and intercostal blocks for post-thoracotomy pain in 45 patients divided into three groups and found similar levels of pain, opioid requirements, pulmonary function and adverse effects.

INTRAPLEURAL ANALGESIA

Intrapleural analgesia arises as a result of injection of local anaesthetic between the pleurae (compared with outside the parietal pleura with paravertebral analgesia). Almost all studies have shown a lowering of pain scores and opioid requirements. More objective measures such as the study of postoperative pulmonary function have not conclusively shown any improvement with intrapleural blocks.[52 56 67] In a prospective randomized comparison of post-thoracotomy pain managed with paravertebral or intrapleural analgesia involving 53 patients, we found that pain scores were the same but pulmonary function was significantly worse with intrapleural blocks.[76] We questioned whether respiratory muscle function was being actively impaired by gravity-dependent pooling of local anaesthetic on the diaphragm as we routinely nurse our postoperative patients in the sitting position.[97] Bupivacaine after intrapleural administration is known to be avidly taken up by the diaphragm.[98] Dependent chest drain losses of local anaesthetic, which can be approximately 30% to 40% with intrapleural blocks,[25] are much less with paravertebral infusion.[81] For this reason we have questioned the continued use of intrapleural analgesia for post-thoracotomy pain relief.[74 76]

Intrapleural analgesia is known to be positional and it is generally recommended that patients are nursed supine,[33 52 54 56 67] temporarily after bolusing, or continuously in the case of infusions. We challenge the wisdom of this approach to postoperative care as it would mitigate against maintenance of functional residual capacity and accelerated mobilisation regimens.[36 84 86] Paravertebral administration does not radiologically or clinically respond as if it is gravity dependent.[24 74 76 81] Qualitative differences also separate these techniques. Lack of block of the posterior ramus of the intercostal nerve with intrapleural analgesia means that after thoracotomy, patients can suffer from pain from the proximal wound edge and from damaged vertebral muscles and ligaments.[25] In clinical settings other than after thoracotomy, it does not appear that these two techniques have been directly compared.

The risk of pleural or pulmonary damage with intrapleural blocks[99] is greater than with paravertebral techniques as pleural penetration is necessary for intrapleural catheterization. An accurate incidence of pneumothorax is difficult to determine as it depends upon efficient reporting of this complication. In retrospective literature reviews, there was a 2% incidence of pneumothorax with intrapleural blocks[99] compared with a 0.5% incidence with paravertebral blocks.[71] A prospective, multiple-centre study agreed with the latter figure.[48]

Contraindications

Paravertebral blocks have a low potential for neurological damage. Except in the case of inadvertent extradural or intrathecal entry, or the use of neurolytic agents, damage to nervous structures other than peripheral (spinal or intercostal) nerves has not (to our knowledge) occurred. Paravertebral blocks can be safely performed in anaesthetized patients. Because of the low potential for neurological damage, the presence of a coagulation disorder or the use of anticoagulants are relative rather than absolute contraindications: the neurological consequences of a paravertebral haematoma are probably small, especially if compared with an extradural haematoma. In a number of patients undergoing major lung or oesophageal resection who have been fully anticoagulated we have successfully used paravertebral analgesia. Venous puncture has been recorded in one patient which required no specific treatment.[44]

Local sepsis at the proposed site is a contraindication, as is sepsis in the chest cavity, for example, an empyema. Pus between the pleurae should not theoretically be disturbed by paravertebral cannulation but the accompanying acidosis would be expected to adversely effect local anaesthetic ionization (and hence nerve penetration) and any accompanying hyperaemia would encourage its systemic absorption. Occupation of the paravertebral space by tumour is also a contraindication although a chest wall tumour lateral to the paravertebral space is not. Care is needed in the case of severe chest deformity or scoliosis to avoid injection into the meninges or pleura.

A planned pleurectomy is not a contraindication. As long as the parietal pleura covering the vertebral bodies and a few centimetres distally is left intact, catheterization and a satisfactory block can be achieved.[60]

Side effects and complications

Paravertebral blocks generally have a low incidence of adverse effects. In retrospectively reviewing this subject, we estimated that the overall incidence of side effects or complications was less than 5%.[71] In a multiple-centred, prospective study of 367 paediatric and adult patients, we found an overall failure rate of 10.1%. The frequency of complications was: hypotension 4.6%; vascular puncture 3.8%; pleural puncture 1.1%; and pneumothorax 0.5%.[48]

Neurological or haemodynamic complications from accidental extradural or intrathecal entry have not been associated with any long-term morbidity or mortality, even after total spinal anaesthesia.[26 93] Three patients (out of 206 injections) in one of these studies developed postural headaches indicating that meningeal trauma had probably occurred.[93] The most serious complication ever reported was a Brown Sèquard paralysis which followed the use of paravertebral alcohol for the treatment of angina pectoris in 1931.[57] At that time, this frequently used destructive treatment would not have involved radiological screening.[102]

Accidental extradural injection is a rare event[51 71] which indicates a faulty technique. Extradural spread of local anaesthetic can occur but it is not known whether or not this event contributes to the block. Occasionally a 1 or 2 dermatome contralateral block occurs but only rarely is a fully bilateral block observed. It is possible that injection inferior to the transverse process, directly adjacent to an intervertebral foramen, encourages this phenomenon.[66]

A unilateral Horner's syndrome means spread up to the cervical region has occurred. It is not itself a cause for concern, although the patient will need reassurance. The unique case of a bilateral Horner's syndrome is disconcerting.[66] The actual spinal level of injection was not stated. Anterior vertebral spread of solution may have occurred,[46] or else there may have been some cross-over of sympathetic fibres. A bilateral block, if it is associated with a bilateral phrenic nerve or recurrent laryngeal nerve block, would be dangerous. However, there are no data as to whether a posterior approach to the stellate ganglion (via a paravertebral injection) is more or less hazardous in this respect than the more frequently used anterior approach.

Segmental thoracic pain has been observed in one patient after cholecystectomy and caused chronic pain for three months,[5] the likely cause being intercostal nerve trauma. This event is probably quite common, but a surgical incision within the same or an adjacent dermatome with its associated acute and possibly chronic pain makes the diagnosis of needle or catheter intercostal nerve damage difficult. Urinary retention is not a problem, either from our experience or from published studies.

The haemodynamic consequences of a correctly placed bolus of local anaesthetic in a normally hydrated patient are minimal.[14 71] A study of thoracic paravertebral blocks using 0.5% bupivacaine 15 ml produced a mean unilateral sympathetic block of 8 dermatomes but without any significant change between supine and sitting arterial pressures.[14] The occurrence of hypotension in 4.6% of (mainly) perioperative blocks (see above) may be multifactorial, with unmasking of relative hypovolaemia by unilateral vasodilatation.

Discussion

We believe that paravertebral blocks are effective and safe, although this may not be the commonly accepted view in the anaesthetic literature. We are unable to explain this difference of interpretation, but counsel that descriptions of paravertebral blocks as "ineffective and hazardous",[2, 22] or lack of descriptions of the technique in textbooks[100] should no longer be allowed to suppress interest and research in this technique. At the beginning of this century, it was thought that more central forms of afferent block were not completely effective and had life-threatening complications. This situation may not have substantially changed.[1 8 9 21 65 68 91] No ideal regional anaesthetic block exists; all must be carefully compared. Paravertebral blocks are relatively easy to learn, they have few contraindications and require no additional nursing surveillance. They are applicable to large numbers of patients and, because of their low side-effect profile (especially hypotension), they contribute to accelerated postoperative mobilization regimens. "Is it (yet) time for revivification of paravertebral blocks?".[69]

Acknowledgement

We dedicate this review to the memory of the surgeon, Emeritus Hunterian Professor Sabaratnam Sabanathan. A great proponent of paravertebral nerve blocks, a great scientist and a great friend.

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SHORT COMMUNICATIONS

Jugular venous desaturation following cardiac surgery†

M. J. SOUTER, P. J. D. ANDREWS AND R. P. ALSTON

Summary

Twenty-two patients undergoing coronary artery bypass surgery underwent postoperative measurement and recording of jugular venous oxyhaemoglobin saturation (Sj_{O_2}) with desaturation defined as a value of less than 50% for 5 min or longer. Fifteen of the 22 patients monitored experienced desaturations. An average of four episodes were experienced by those 15 patients (range 1–14). The mean duration of a single episode was 46 (range 5–212) min whilst mean total duration of desaturation was 175 (range 5–570) min. The mean duration of desaturation in the 15 patients, expressed as a percentage of monitored time, was 21.1% (range 0.58%–61.96%). Sj_{O_2} desaturation, possibly indicating cerebral hypoperfusion, occurs in the early postoperative period following cardiac surgery. (*Br. J. Anaesth.* 1998; **81**: 239–241)

Keywords: surgery, cardiac; complications; equipment, continuous in vivo oximetry; monitoring, jugular bulb oxygen saturation

Brain damage, ranging from stroke to cognitive dysfunction, is an important complication of cardiac surgery.[1-3] The epoch of injury has commonly been assumed to be the intra-operative period. However, cerebral oedema and vasoconstriction occur in the early postoperative period which suggests that cerebral injury could also be occurring at this time.[4 5]

During cardiac surgery, jugular venous oxyhaemoglobin (Sj_{O_2}) desaturation has been noted during several phases of normothermic and hypothermic cardiopulmonary bypass (CPB).[6-9] Most importantly, Sj_{O_2} desaturation during rewarming has been associated with cognitive dysfunction.[10] We hypothesized that cerebral hypoperfusion may be occurring in the early postoperative period and that it may be identifiable by Sj_{O_2} monitoring. The aim of this study was to determine whether Sj_{O_2} desaturation occurs postoperatively following cardiac surgery and, if so, to quantify the magnitude of such events.

Methods and results

After obtaining local ethical committee approval, informed consent was obtained from 22 patients scheduled for elective coronary artery bypass surgery.

Anaesthesia and ICU: Premedication was with lorazepam 1–4 mg orally at 10 pm on the night before surgery, then temazepam 20–30 mg orally 1 h induction. Anaesthesia was induced with midazolam up to 0.2 mg kg^{-1}, fentanyl 5 μg kg^{-1} and etomidate as required to abolish the eyelash reflex. Neuromuscular block was obtained using pancuronium 0.15 mg kg^{-1}. Anaesthesia was maintained with fentanyl 0.1 μg kg^{-1} min^{-1} and midazolam 0.5 μg kg^{-1} min^{-1}, supplemented with isoflurane. Ventilation was controlled mechanically, before and after CPB, to obtain normocapnia (4.5–5.3 kPa). Following surgery, patients were transferred to the ICU and postoperative care was managed to avoid haemodynamic instability and hypoxia.

Extubation was contingent upon normothermia; stable haemodynamics and absence of significant arrhythmias; the patient awake and moving all four limbs to command without residual neuromuscular block; mediastinal blood loss less than 100 ml h^{-1}; Pa_{O_2} greater than 8 kPa with an $F_{I_{O_2}}$ of 40%; and Pc_{O_2} less than 8 kPa with a spontaneous rate of greater than 8 breaths per minute.

Cardiopulmonary bypass: The CPB circuit consisted of a membrane oxygenator and a non-pulsatile roller pump and was primed with lactated Ringer's solution 2 litres, and sodium bicarbonate 50 mmol. Acid base management was according to alphastat principles. Non-pulsatile flow was used at a rate of 2.4 litres min^{-1} m^{-2}. Moderate hypothermia (nasopharyngeal temperature 28 °C) was used. Mean arterial pressure (MAP) was controlled between 50–90 mm Hg using boluses of methoxamine 2 mg or phentolamine 1 mg as required.

Jugular bulb oximetry: Immediately after induction of anaesthesia, the right jugular vein was cannulated retrogradely and a spectrophotometric catheter (Opticath, Abbott Laboratories, Maidenhead, Berkshire, UK) inserted to lie in the jugular bulb. Catheter position was confirmed radiologically. The catheter was connected to a Oximetrix 3 System (Abbott Laboratories, Maidenhead, Berkshire, UK). The reading obtained was then calibrated *in vivo* against jugular venous samples analysed by a Corning 270 Co-oximeter. After surgery, the patient

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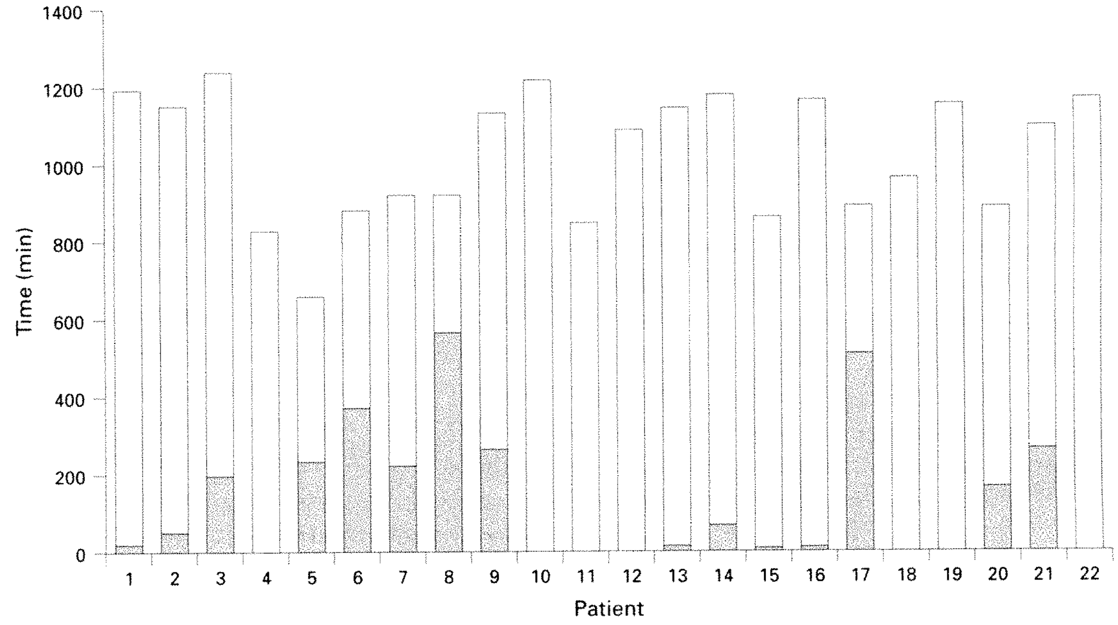

Figure 1 Total insult time with monitored time. Shaded area=total insult time; unshaded area=total monitoring time.

was transferred into the ICU, and the Sj_{O_2} catheter recalibrated. Monitoring was terminated on the day after surgery when patients were transferred out of the ICU.

Statistical analysis: Cerebral hypoperfusion was defined as an Sj_{O_2} less than 50% for five consecutive minutes.[7,9] Data analysis was by analysis of variance (ANOVA) and the Kruskal-Wallis test, using SPSS-PC (SPSS Inc., Michigan, USA) and EPI-INFO (Center for Disease Control, Atlanta, Georgia, USA).

Sixteen males and six females were studied, and an average of three grafts per patient (range 2–4) performed. The mean age was 59 years (95% CI: 56, 62) with a mean height of 169 cm (95% CI: 166, 173) and weight of 77 kg (95% CI: 72, 81), giving a mean calculated BSA of 1.87 (95% CI: 1.81, 1.94). The duration of aortic cross-clamping was 46 min (95% CI: 41, 50), and the duration of CPB was 81 min (95% CI: 74, 87).

Postoperative monitoring was used for a mean time of 1025 min (95% CI: 95, 1093). Fifteen of the 22 patients monitored experienced 65 Sj_{O_2} desaturations over the postoperative monitoring period. In those 15 patients, (i) the mean duration of a single episode was 46 min (95% CI: 34, 56) with a range of 5 to 212 min; (ii) the mean total duration of cerebral desaturation suffered was 197 min (95% CI: 106, 289) with a range of 5 to 570 min; (iii) the mean total desaturation expressed as a percentage of total time monitored postoperatively was 21.1% (95% CI: 10.8, 31.4); (iv) an average of four episodes were suffered by those patients experiencing cerebral hypoperfusion (range 1–14).

For all 22 patients monitored, the mean duration of cerebral desaturation expressed as a percentage of monitoring time was 14.4% (95% CI: 6.3, 22.5) with a range of 0.58% to 61.96%. Figure 1 expresses total duration of desaturation in relation to total time of monitoring in each patient.

The mean of the highest Sj_{O_2} value recorded was 81% (range 72–90), and the mean of the lowest was 37% (range 12–52).

The mean time from the last calibration of the monitoring system to onset of the first desaturation was 181 min (95% CI: 9, 354 min). Fifty-one of the 65 episodes commenced within 12 h of transfer to ICU, whilst all desaturations had terminated by 18 h after transfer. Fifty had terminated within 12 h. The mean time of the last desaturation terminating was 666 min from transfer (95% CI: 483, 849 min).

Ten patients received inotropes postoperatively. Twenty-one of the 22 patients were extubated within 24 h with a mean time from transfer to extubation of 656 min (95% CI: 525–788 min) One patient was ventilated for three days, and was the only patient reopened for postoperative bleeding (with no desaturations). Eight patients experienced Sj_{O_2} desaturations before extubation, with three after, and four both before and after extubation. There were no recorded episodes of systemic hypoxia, seizure or pyrexia. There was no evident association between the jugular desaturations and (i) either the administration and timing of analgesia or inotropes; (ii) the time of extubation, or (ii) the presence of hypotension as recorded on the nursing records.

Comment

The Oximetrix Sj_{O_2} monitoring system has been criticized because it exhibits calibration drift.[11] However, it has a 12-h period of accurate recording, with 5% limits of agreement between catheter and co-oximeter measurements. Although we did not recalibrate at 12 h, it is unlikely that the desaturations in the present study are a result of drift as the vast majority of desaturations started and finished within 12 h of calibration.

The mechanism of the desaturations in Sj_{O_2} found in this study is unclear. Desaturation is the consequence of relative cerebral hypoperfusion. Cerebral oedema and vasoconstriction have been found to occur in the early postoperative period following cardiac surgery and both could produce an imbalance between cerebral oxygen supply and demand.[4 5] Derangement of systemic haemodynamics and oxygenation could be important, despite a seeming independence of desaturations from the haemodynamic and ventilatory events noted. However, because of the periodic nature of the nursing observations used, the possibility remains that suboptimal levels of systemic arterial pressure or oxygenation may have provoked the desaturations, as these parameters were not prospectively recorded, and transient insults may have gone undetected. Pyrexia or seizure induce hypermetabolism and increase oxygen consumption, but there was no evidence of either. Further investigation is required to accurately determine whether there is any association between Sj_{O_2} desaturations and systemic haemodynamics and oxygenation.

The duration of Sj_{O_2} desaturations in the present study by far exceed those recorded by Andrews and Colquhoun, the only study so far to chronicle the duration as well as the degree of desaturation intraoperatively.[9] They noted a mean duration of 27 min when Sj_{O_2} was less than 50%, with a range of 4 to 51 min and a maximum desaturation to 19%. In the present study, the mean total postoperative duration of desaturation was 197 min (95% CI 106, 289) which is over six times longer. If these postoperative Sj_{O_2} desaturations do represent cerebral hypoperfusion then it may be that cerebral damage is occurring in the early postoperative period. Additionally, analogous to the established deleterious effect of secondary physiological insult upon head injuries,[12] intraoperative cerebral damage may be being exacerbated by secondary hypoperfusion insults postoperatively. Although Croughwell and colleagues have found that low Sj_{O_2} during surgery is associated with decrements in cognition,[10] further prospective investigation is required to determine whether there is any association between postoperative Sj_{O_2} desaturations following cardiac surgery and brain damage.

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Effects of resuscitation fluids on T cell immune responses

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Summary

This study was designed to determine whether dextran, gelatin or hydroxyethyl starch-based colloidal resuscitation fluids (CRF) are inhibitory to T lymphocyte activation and mitogenesis *in vitro*. Isolated peripheral blood lymphocytes from normal donors were activated with mitogen (PHA) and cultured in up to 50% v:v CRF. Dual-label flow cytometry for CD69 and CD25 were used to assess early and full T cell activation responses, respectively, and thymidine incorporation was used to assess mitogenesis. T cell activation and mitogenic responses were not inhibited in the presence of CRF, implying that any systemic immunodepression associated with CRF infusion is not directly related to CRF-mediated impairment of T cell activation. (*Br. J. Anaesth.* 1998; **81**: 242–243)

Keywords: blood, T cells, immune response, suppression; fluids, colloidal resuscitation; blood, haemodilution

Hydroxyethyl starch (HES) has been used as a cryoprotectant and a resuscitation fluid. Recent developments in red blood cell cryopreservation use these dual functions of HES to allow the direct infusion of thawed blood without prior washing.[1] As transfusion alone is immunosuppressive, it is important to ensure that agents used in treatment, such as resuscitation fluids, do not exacerbate any depression of systemic immune function. This consideration particularly applies to HES, where residual amounts are known to persist in the intravascular space for extended periods, relative to other colloidal resuscitation fluids.[2] Specific data about the effects of colloidal resuscitation fluids on the adaptive immune system are limited. Patient outcome after clinical use of HES as a volume expander in situations of multisystem trauma and shock has been satisfactory.[3] However, HES can impair the non-adaptive immune response in mice by reducing phagocytic clearance.[4] Nevertheless, we have not been able to demonstrate any significant inhibition of neutrophil activation nor of phagocytosis of opsonized bacteria by neutrophils and monocytes in humans *in vitro*.[5] However, lymphocyte function has not been extensively examined in humans and it remains unclear as to whether resuscitation fluids might impair post-transfusion immune responses via lymphocyte-mediated pathways. This study was designed to investigate whether commonly used colloidal resuscitation fluids (CRF) are directly inhibitory to T lymphocyte activation. In order to minimize confounding variables such as immunosuppression resulting from trauma alone, isolated peripheral blood mononuclear cells from healthy volunteers were studied. Early and intermediate points in the activation cascade were examined, together with entry into the mitotic cycle. Because lymphocytes require functional accessory cells for mitogenic responses, blastogenesis assays also measure accessory cell function *de facto*, thereby providing additional information about part of the non-adaptive immune response.

Methods and results

Peripheral blood lymphocytes from healthy volunteers (n=15, median age=34 yr) were isolated by density barrier centrifugation and cultured in 96-well tissue culture plates with 2.5 μg ml^{-1} phytohaemagglutinin (PHA), as described previously.[6] Negative controls of unstimulated cells were included for each experiment. Cell cultures were also established in media containing dilutions of the resuscitation fluids, colloidal substances at various concentrations in isoionic solution, which were added to the culture media to final concentrations of 6.25%, 12.5%, 25% and 50% (v:v) of the solutions as supplied.

Cells were cultured with or without mitogen and with or without CRF which comprised hydroxyethyl starch (Hespan; Du Pont Pharma, Herts, 6%, 450,000 Mr polymer), Dextran 70 (Macrodex, Kabi Pharmacia Ltd., Bucks, 6%, 70,000 Mr polymer) and two gelatin preparations (Gelofusine, Vifor UK Ltd, Chester, 4%, 30,000 Mr polymer and Haemaccel, Hoechst UK Ltd, Middlesex, 3.5%, 35,000 Mr polymer). Phosphate-buffered saline (PBS) was used as a dilution control.

Expression of T cell activation markers was assessed by two-colour flow cytometry, as described previously.[6] Duplicate tubes were used for all experiments. Antibodies used were phycoerythrin (PE)-conjugated anti-CD2 (Dako Ltd., Bucks) to indicate the T-cell fraction and either fluorescein (FITC)-conjugated anti-CD69 (Dako) or FITC-conjugated anti-IL-2 receptor α-chain (CD25) (Dako). CD2, although also expressed at low density on NK cells, was used in preference to CD3 as CD3 is down-regulated following T cell activation. PE and FITC-conjugated antibodies against *Aspergillus niger* glucose oxidase (Dako) were used as controls. Flow cytometry was performed on a FACScan analytical instrument (Becton Dickinson Ltd., Oxford) and a 'gate' was drawn around the CD2$^+$ T cell population

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to exclude non-T cells. Results were expressed as the median fluorescence channel value of the cell population as an arbitrary measure of receptor density.

Entry of cells into S-phase was assessed by measuring 18-h incorporation of DNA precursor at 72 h. 0.5 μCi of ^{3}H-thymidine (Amersham, Bucks) was added to each well and incorporation was measured by liquid scintillation spectrometry. The results were expressed as a stimulation index (SI) = (test count/min)/(control count/min) after subtraction of background counts.

Resting T cells cultured with CRF or PBS, but without PHA, showed no alteration in the expression of CD69, CD25 or mitotic response relative to controls.

CD69 expression on resting T cells was negligible and peaked at 24 h after stimulation, when ≥75% of CD2$^+$ cells became positive with a median fluorescence channel of approximately 100. CRF had no significant effect on the percentage of cells becoming activated, nor on the median intensity of CD69 expression (table 1). CD25 expression was very low on resting T cells, with less than 5% of T cells falling into the positive 'gate'. Mitogen-induced upregulation of CD25 peaked at 72 h, with ≥95% of T cells expressing CD25 with a median fluorescence intensity of approximately 700. CRF did not significantly inhibit upregulation of CD25 (table 1). Dilution with PBS had no significant effect on T cell activation. The incorporation of thymidine was not significantly affected by CRF or PBS and Stimulation indices were very close to the control values for PHA-activated cells in growth medium only (table 1). No significant or consistent differences were found between donors and comparable results were obtained when the same donors were re-tested on subsequent occasions.

Comment

T cell activation and mitogenesis involves a complex cascade of events requiring inputs from accessory cells in the form of cytokines and cell-surface ligand/receptor interactions. Our results demonstrate unequivocally that the early, intermediate and late events of this cascade are unimpaired by CRF. The findings also imply that accessory cell function remains unaffected.

By studying T cell responses from healthy volunteers in a controlled *in vitro* situation, we have sought to minimize confounding variables associated with trauma, such as possible effects on cell pre-activation status or the presence of immunosuppressive serum factors, which are not directly associated with transfusion or blood volume replacement therapy with colloidal resuscitation fluids. Despite previous work implicating colloidal resuscitation fluids as an exacerbating factor in post-trauma immunomodulation, our data demonstrate that the CRF do not directly inhibit major events of the T cell activation cascade.

Table 1 Effects of colloidal resuscitation fluids on mitogen-induced T cell activation, assessed by expression of CD69 (early activation marker) after 24-h culture and CD25 (IL-2 receptor chain; full activation marker) at 72 h, and on mitogenesis, assessed by ^{3}H-thymidine incorporation after 96 h culture The results are expressed as means (SD) of data normalized to the controls, arbitrarily defined as 100. The number of independent determinations (*n*) is indicated. Flow cytometry experiments were performed in duplicate and five replicates were used for ^{3}H-thymidine incorporation assays. None of the results was statistically significantly different from control values (ANOVA with Bonferroni correction)

Resuscitation fluid	Final concentration *in vitro*				
	n	6.25%	12.5%	25%	50%
CD 69					
Macrodex	15	101 (6)	109 (8)	118 (11)	105 (18)
Gelofusine	8	112 (11)	116 (18)	119 (23)	118 (28)
Haemaccel	9	93 (14)	88 (15)	92 (14)	83 (13)
Hespan	9	114 (22)	126 (30)	124 (37)	112 (39)
CD 25					
Macrodex	15	98 (9)	97 (9)	91 (13)	86 (15)
Gelofusine	13	108 (9)	106 (14)	104 (8)	89 (9)
Haemaccel	6	104 (12)	103 (11)	98 (9)	94 (13)
Hespan	8	100 (8)	96 (11)	94 (9)	89 (11)
Stimulation index					
Macrodex	14	115 (47)	166 (157)	177 (159)	210 (181)
Gelofusine	13	108 (10)	141 (±76)	141 (45)	193 (82)
Haemaccel	6	101 (9)	98 (9)	108 (11)	101 (19)
Hespan	8	90 (8)	91 (10)	88 (11)	79 (10)

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Mechanical and electrophysiological effects of mepivacaine on direct myocardial depression *in vitro*

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Summary

The effects of various concentrations (20, 50, and 100 μmol litre^{-1}) of mepivacaine were studied in isolated guinea pig and rat right ventricular papillary muscles by measuring the effects on myocardial contractility and electrophysiological parameters. Mepivacaine produced dose-dependent depression of peak force during 0.5 to 3 Hz stimulation rates in guinea pig papillary muscles. Conduction block was frequently noted, especially at higher stimulation rates (2 and 3 Hz) with mepivacaine 50 and 100 μmol litre^{-1}. In rat papillary muscle experiments, about 20% depression of peak force was shown at rested state contraction. Shortening of action potential (AP) duration (APD_{50}: about 10%, APD_{90}: about 10%) and rate-dependent depression of d*V*/d*t* max was observed with mepivacaine 100 μmol litre^{-1}. In 26 mmol litre^{-1} K^+ Tyrode's solution, mepivacaine 50 and 100 μmol litre^{-1} produced a dose-dependent depression of early (50 μmol litre^{-1}: about 20%, 100 μmol litre^{-1}: about 30%) and late (50 μmol litre^{-1}: about 30%, 100 μmol litre^{-1}: about 50%) force development. In slow APs, neither shortening of AP duration nor changes of d*V*/d*t* max were shown by mepivacaine 100 μmol litre^{-1}. An approximate 30% depression of contracture induced by rapid cooling after 2 Hz stimulation rates was observed with mepivacaine 100 μmol litre^{-1}. It may be concluded that the direct myocardial depressant effect of mepivacaine is likely to be caused by inhibition of Ca^{2+} release from the sarcoplasmic reticulum. The Na^+ channel blocking action may contribute indirectly to the depression of contractility. (*Br. J. Anaesth.* 1998; **81**: 244–246)

Keywords: anaesthetics local, mepivacaine; muscle cardiac, contractility; muscle cardiac, action potential; muscle cardiac, rapid cooling contracture; muscle cardiac, sarcoplasmic reticulum; model, rat; model, guinea pig

In vivo[1] and *in vitro*[2] animal studies have shown that local anaesthetics produce dose-related depression of cardiac output or negative inotropic action with minimal changes in peripheral vascular resistance. Although the electrophysiological basis of local anaesthetic action is block of sodium channels, the mechanisms of myocardial depression may involve additional actions indirectly related to the regulation of intracellular calcium such as Ca^{2+} entry into the cell or Ca^{2+} release from the sarcoplasmic reticulum. Mepivacaine, an amide local anaesthetic agent with potency similar to lidocaine, has been reported to show clinical effects similar to lidocaine, although it is closely related in chemical structure to bupivacaine. Although the negative inotropic effect of mepivacaine has been reported in an *in vivo* study,[1] direct myocardial depression has not yet been defined. Therefore, the purpose of this study was to determine the degree and mechanisms of direct myocardial depression produced by mepivacaine.

Methods and results

EXPERIMENT WITH NORMAL K^+ TYRODE'S SOLUTION

According to a procedure approved by the Yonsei University College of Medicine Animal Research Committee, the right ventricular papillary muscle was removed from female guinea pigs (300–400 g) or Sprague–Dawley rats (300–400 g) after intraperitoneal pentobarbital sodium injection (50 mg kg^{-1}). The tendinous end of the muscle was attached by a strut to a GRASS FT03 force transducer. The bath was superfused at 37°C at a rate of 8 ml min^{-1} with normal Tyrode's solution (mmol litre^{-1}: Na 143, K 5, Ca 2, Cl 127, $MgSO_4$ 1.2, HCO_3^- 25, glucose 11, Ethylenediaminetetraacetic acid (EDTA) 0.1) bubbled with 95% oxygen/5% carbon dioxide maintaining mean pH (SD) at 7.4 (0.5). The muscles were field-stimulated by a GRASS S44 stimulator (GRASS Instruments, Quincy, MA, U.S.A.).

Membrane potential and its rate of rise during the action potential (dV/dt max) was monitored by a conventional 3 M KCl-filled glass microelectrode (10–20 MΩ) attached to a WPI VF-1 preamplifier. In rat experiments, the contractile response to 100 μmol litre^{-1} mepivacaine in normal Tyrode's solution only was observed. As rat papillary muscle showed progressive deterioration of contractility over time, time control experiments were performed separately to those of mepivacaine administration.

Whereas mepivacaine 20 μmol litre^{-1} caused contractile depression at 1–3 Hz stimulation rates, mepivacaine 50 and 100 μmol litre^{-1} showed depression at all stimulation rates. Effects of 50 μmol litre^{-1} were greater than those of 20 μmol litre^{-1}, and effects of 100 μmol litre^{-1} were greater than those of mepivacaine

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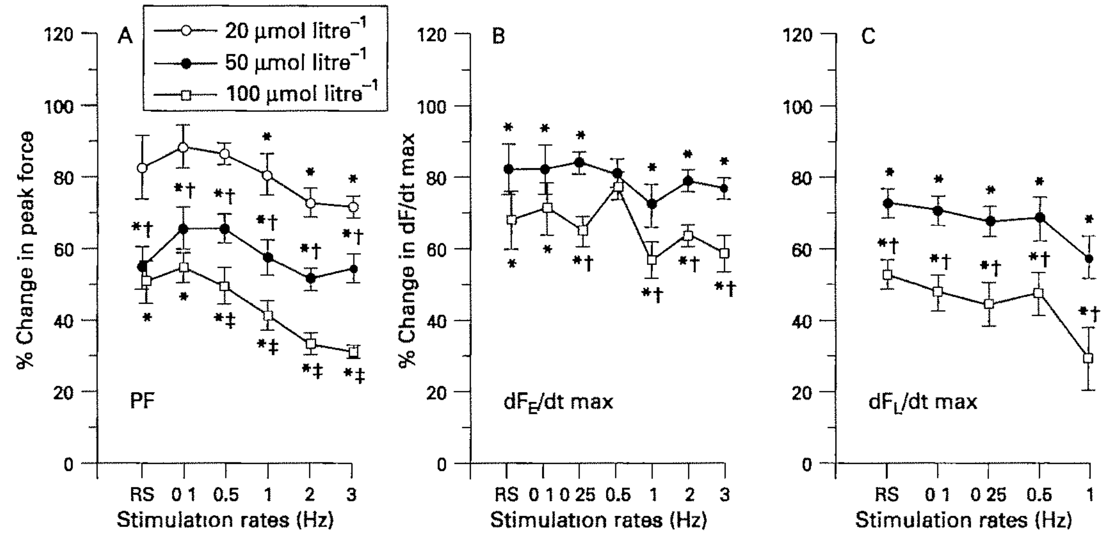

Figure 1 (A) Effects of increasing concentrations of mepivacaine on peak force (PF) in normal K^+ Tyrode's solution at various stimulation rates in guinea pig papillary muscles. Results are plotted as mean (SEM) percentage of control ($n=7$). *, †, and ‡ indicate differences ($P<0.05$) from control, mepivacaine 20 µmol $litre^{-1}$, and 50 µmol $litre^{-1}$, respectively (ANOVA). (B) Effects of mepivacaine 50 and 100 µmol $litre^{-1}$ on the maximum rate of early force development (dF_E/dt max) ($n=5$) in 26 mmol $litre^{-1}$ K^+ Tyrode's solution with isoprenaline 0.1 µmol $litre^{-1}$ at various stimulation rates in guinea pig papillary muscles. (C) Effects of mepivacaine 50 and 100 µmol $litre^{-1}$ on the maximum rate of late-force development (dF_L/dt max) ($n=5$) in 26 µmol $litre^{-1}$ K^+ Tyrode's solution with isoprenaline 0.1 µmol $litre^{-1}$ at RS–1 Hz stimulation rates in guinea pig papillary muscle. Results are plotted as mean (SEM) percentage of control. *, † Indicate differences ($P<0.05$) from control and mepivacaine 50 µmol $litre^{-1}$, respectively (ANOVA).

50 µmol $litre^{-1}$ from 0.5 to 3 Hz stimulation rates. Contractile depression at 2–3 Hz was greater than that at rested state (RS)–0.1 Hz with mepivacaine 100 µmol $litre^{-1}$ (fig. 1A).

With mepivacaine 20 µmol $litre^{-1}$, the contraction of guinea pig papillary muscles responded normally to field stimulation at all stimulation rates. While mepivacaine 50 µmol $litre^{-1}$ showed a normal contractile response at low stimulation rates (RS–1 Hz), stimulation block was frequently observed at higher stimulation rates (2, 3 Hz). Block of stimulation was frequently observed at all stimulation ranges except RS with mepivacaine 100 µmol $litre^{-1}$. Drug washout for 15 min resulted in satisfactory stimulation resulting from the control voltages at all stimulation rates.

In rat papillary muscles, mepivacaine 100 µmol $litre^{-1}$ produced contractile depression (about 20%) at RS.

In normal action potential (AP) experiments, mepivacaine 100 µmol $litre^{-1}$ produced shortening of APD_{50} and APD_{90} (0.5 Hz: about 18%, 1 Hz: about 12%, 2 Hz: about 7%) from 0.5 to 2 Hz stimulation rates. Mepivacaine 100 µmol $litre^{-1}$ significantly depressed dV/dt max from 0.5 to 3 Hz, and rate-dependent depression of dV/dt max was shown at 2 and 3 Hz stimulation rates. There was no tendency for the muscles to depolarize.

EXPERIMENTS WITH 26 MMOL LITRE^{-1} K^+ TYRODE'S SOLUTION

Muscle force and APs were also studied in 26 mmol $litre^{-1}$ K^+ Tyrode's solution (mmol $litre^{-1}$: Na 122, K 26, Cl 121, Ca 2, $MgSO_4$ 1.2, HCO_3^- 25, glucose 11, EDTA 0.1) with isoprenaline 0.1 µmol $litre^{-1}$. A sequential increase in stimulation rates from rest to 1 Hz was performed. Increasing concentrations of mepivacaine (50 and 100 µmol $litre^{-1}$) were applied sequentially in contraction studies, and mepivacaine 100 µmol $litre^{-1}$ was only used to assess the drug effect in slow APs.

Early force development was depressed by about 30% and 45% with mepivacaine 50 and 100 µmol $litre^{-1}$, respectively (fig. 1B). In the late developing force, mepivacaine 50 and 100 µmol $litre^{-1}$ caused an approximate 25% and 50% depression, respectively (fig. 1C). Stimulation block was not observed. Mepivacaine 100 µmol $litre^{-1}$ caused neither change in resting membrane potential, slow AP amplitude, and dV/dt max, nor shortening in AP duration at 0.1, 0.25, 0.5, and 1 Hz stimulation rates.

RAPID COOLING CONTRACTURE EXPERIMENTS

After the 15-min rest at 37 °C, rapid cooling was induced by perfusion at a flow rate of about 50 ml min^{-1} with 0 °C normal Tyrode's solution (<5 °C achieved within 1.5 s) in which 95% oxygen/5% carbon dioxide was bubbled. Following the measurement of RS rapid cooling contracture, the chamber was changed to normal Tyrode's solution at 37 °C. After full rewarming to 37 °C, stimulation at 0.1 Hz, followed by 1 and 2 Hz stimulation rates, was sequentially applied until maximal and stable contractions were elicited after 2 Hz. Rapid cooling was induced again. Following control measurements, muscles were exposed to mepivacaine 100 µmol $litre^{-1}$ for 15 min at 37 °C before eliciting the rapid cooling contracture.

After 15-min rest, there was no change in RS rapid cooling contracture with mepivacaine 100 µmol $litre^{-1}$. Peak force at 2 Hz contraction was diminished to about 58% of control by mepivacaine 100 µmol $litre^{-1}$, while contracture was depressed from 5.11 to 3.86 mN mm^{-2} (about 70% of control). Time to peak contracture remained unchanged (control: 13.6 s, 100 µmol $litre^{-1}$ 14.5 s).

In force studies, mean cross-sectional areas were 0.81 (0.29) (mean (SD), $n=40$) and 0.88 (0.45) mm^2 (mean (SD), $n=13$) in guinea pigs and rats, respectively.

Repeated measures of analysis of variance (ANOVA) followed by Fisher PLSD multiple range test was applied to test for significant differences in the stimulation rates and among the mepivacaine concentrations. A P value <0.05 was considered significant.

Comment

Moderate depression by mepivacaine of cardiac output and stroke volume (about 15%) with little change in systemic vascular resistance has been reported in an *in vivo* animal study. Although etidocaine and bupivacaine caused more marked depression of cardiac output (about 50% and 100%, respectively), lidocaine showed modest depression at the same dose.[1] In the present study, mepivacaine 50 μmol litre^{-1} caused an approximate 40% depression of peak force, which was comparable to that of lidocaine 40 μmol litre^{-1} in a previous guinea pig papillary muscle study.[2]

Our results in normal Tyrode's solution demonstrated that depression of myocardial contractility and frequency-dependent block of dV/dt max are more pronounced at higher (2, 3 Hz) stimulation rates with mepivacaine 100 μmol litre^{-1}. The block of Na^+ currents at higher frequencies may account in part for the more decreased contractile depression observed in guinea pig ventricular muscle at 2 and 3 Hz.

The present results of force development in 26 mmol litre^{-1} K^+ Tyrode's solution suggest the inhibition of the two different Ca^{2+} release sites on the sarcoplasmic reticulum membrane activated by depolarization which results from the inhibition of Ca^{2+} efflux from the sarcoplasmic reticulum and/or depression of Ca^{2+} entry.[3] Depression of Ca^{2+} entry may contribute to decreased Ca^{2+} content in the sarcoplasmic reticulum and may have subsequently caused the depression of late developing force. Based on the modest depression of Ca^{2+} influx by mepivacaine, the present biphasic contractile depression may be caused mainly by inhibition of Ca^{2+} release from the sarcoplasmic reticulum. In rat papillary muscles, an approximate 20% depression of RS contraction by mepivacaine 100 μmol litre^{-1} when compared with control also provides further supporting evidence for inhibition of Ca^{2+} release from the sarcoplasmic reticulum.

Cerebral symptoms suggesting systemic intoxication during caudal analgesia have been reported to be associated with a mean mepivacaine concentration in blood of 6.27 μg ml^{-1} (25.48 μmol litre^{-1}).[4] If we assume that the protein binding of mepivacaine at this concentration is approximately 40%,[5] the free plasma concentration will be estimated as 3.76 μg ml^{-1} (15.28 μmol litre^{-1}). As the therapeutic concentrations of mepivacaine observed after a lumbar extradural administration range from 4 to 6 μg ml^{-1} (5.69–8.54 μmol litre^{-1} if we assume 65% protein binding at this range of concentration),[6] this free drug concentration is unlikely to cause myocardial depression. However, in the case of inadvertent administration of mepivacaine, the transient increase in blood concentration may produce cardiac contractile depression if we consider peak blood concentration of lidocaine to be about 30 μg ml^{-1} (128 μmol litre^{-1}) when 3 mg kg^{-1} was injected i.v.[7]

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Comparison of ropivacaine with bupivacaine for paediatric caudal block

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Summary

In a double-blind, multicentre study 245 children aged 1–10 yr undergoing elective minor surgery as inpatients were randomly allocated to receive a single caudal extradural injection of 1 ml kg^{-1} of either 0.25% bupivacaine or 0.2% ropivacaine after induction of light general anaesthesia. The groups were comparable for age, weight, vital signs and duration of surgery. The onset time was similar for ropivacaine and bupivacaine (9.7 *vs* 10.4 min). Further analgesia was not required in 40% of children. The mean time to first analgesia in the remainder was 233 min in the bupivacaine group and 271 min in the ropivacaine group. No motor block was measurable in either group. Ropivacaine 2 mg kg^{-1} was as effective as bupivacaine 2.5 mg kg^{-1} for caudal analgesia in children. (*Br. J. Anaesth.* 1998; **81**: 247–248)

Keywords: anaesthesia, regional, anaesthesia, paediatrics; anaesthetics local, ropivacaine; anaesthetics local, bupivacaine; anaesthetic techniques, extradural

Ropivacaine is a new aminoamide local anaesthetic which in adults appears to cause less motor block and less cardiotoxicity than bupivacaine but produces a similar duration of analgesia.[1] A preliminary evaluation of ropivacaine for caudal analgesia in children suggested a quicker onset and a longer duration of action.[2] The aim of this study was to compare an equal volume of bupivacaine and ropivacaine for caudal analgesia in paediatric patients undergoing subumbilical surgery.

Methods and results

After Ethical Committee approval and parental written informed consent, 245 patients, aged 1–10 yr, ASA I, undergoing elective minor surgery as inpatients were studied (table 1). All patients received oral midazolam 0.5 mg kg^{-1} 30 min before surgery. Sevoflurane, halothane or propofol 2.5 mg kg^{-1} were given for induction and sevoflurane or isoflurane in oxygen/air ($F_{I_{O_2}}$=0.4) were administered for maintenance with spontaneous breathing until the end of surgery. The study used a double-blind methodology with random allocation to the two groups by a computer-generated list. Group B (123 patients) received 0.25% bupivacaine 2.5 mg kg^{-1} (1 ml kg^{-1})[3] and group R (122 patients) received 0.2% ropivacaine 2 mg kg^{-1} (1 ml kg^{-1}) via the caudal route. Heart rate (HR), non-invasive arterial pressure (NIAP) and oxygen saturation by pulse oximetry (Sp_{O_2}) were monitored and recorded during surgery. We evaluated the duration of surgery, the onset of block by pinprick according to the method of Dalens,[3] and the duration of postoperative analgesia using hourly observations of a validated objective pain scale.[4] Rectal paracetamol 20 mg kg^{-1} was given if the score was 6 or more out of 10 and motor block was assessed once on awakening using a four-point Bromage scale. Observations were continued for 24 h by an anaesthetist who was blinded to the local anaesthetic agent administered.

Statistical analysis was performed using the chi-squared test, Student's *t* test and the log-rank test; $P \leq 0.05$ was considered statistically significant. SPSS software was used for the analyses.

The types of surgery are detailed in table 1. The two groups were comparable for age (Group B 4.12 yr [range 1–9]; Group R 4.18 yr [range 1–9 yr]); weight (18.4 kg (SD 6.3) [range 9–30] *vs* 18.1 (SD 6.05) [range 10–28]); and duration of surgery (38 min (SD 16.4) *vs* 37.3 min (SD 16.4)). The mean onset time was 10.4 min (SD 2.3 min) for Group B and 9.7 min (SD 2.2 min) for Group R. No further analgesia was required in 98 of the 245 children (40%), 49 from each group. In the other 147 children, the mean time to first analgesia after bupivacaine was 233.2 min (SD 79.8) compared with 271.9 min (SD 120.9) for ropivacaine (ns). No motor block was seen in either group on awakening. No side effects were seen.

Comment

Previous studies have shown that lidocaine, mepivacaine and bupivacaine all produce relatively short-lived analgesia when given by the caudal route and their action can be prolonged by additives such as epinephrine, opioids, clonidine or ketamine.[5 6]

Recently ropivacaine has been studied in adults for

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Table 1 Type of surgery

	Group B	Group R
Hernia repair	56	48
Hydrocele	10	15
Phimosis	15	13
Orchidopexy	23	27
Hypospadias	19	19
Total	123	122

surgery, Caesarean section, labour and postoperative analgesia. The sensory block produced by ropivacaine is equivalent to bupivacaine but motor block is less intense and shorter in duration.[1] We previously found in a preliminary study in children that 0.2% ropivacaine 2 mg kg^{-1} (1 ml kg^{-1}) produced a more rapid onset and more prolonged analgesia compared with 0.25% bupivacaine 2 mg kg^{-1} (0.8 ml kg^{-1}).[2] In the present study, the dose and volume of bupivacaine was increased to 2.5 mg kg^{-1} (1 ml kg^{-1}) so that equal volumes of solution could be given to maintain the blindness of the study.[3] Low concentrations and large volumes are the key to obtaining differential block in children because of the small diameter of the A-delta and C-fibres and the small distance between the nodes of Ranvier. This study suggests that 0.2% ropivacaine 1 ml kg^{-1} given as a single shot caudal extradural block is equivalent to the same volume of 0.25% bupivacaine. The lower intrinsic toxicity of ropivacaine and lower mass of drug needed gives an increased margin of safety which may be important, particularly in younger children.

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Aging decreases the sensitivity of the GABA carrier to propofol and etomidate†

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Summary

The influence of aging on the pharmacodynamics of anaesthetic agents in the central nervous system remains poorly understood. As α-aminobutyric acid (GABA)-mediated neurotransmission appears to be an important target for anaesthetics in the brain, we hypothesized that aging could alter the sensitivity of the GABA carrier to anaesthetics. We have examined the effects of etomidate and propofol on the uptake of $[^3H]$-GABA (5 min, 37 °C) into striatal synaptosomes of rats aged 2, 18 and 24 months. In 2-month-old rats, $[^3H]$-GABA uptake was inhibited by nipecotic acid, a competitive inhibitor of the GABA carrier (IC_{50} = 3.6 SD 0.3 μM). Etomidate and propofol markedly reduced the activity of the GABA carrier, with IC_{50} values 58 (SD 3) and 46 (SD 3) μmol $litre^{-1}$, respectively. Aging increased IC_{50} values for these anaesthetics. Nipecotic acid was unaffected. These data suggest that aging selectively alters the action of etomidate and propofol in the mammalian CNS. (*Br J. Anaesth.* 1998; **81**: 249–250

Keywords: aging; anaesthetics, i.v., propofol; anaesthetics, i.v., etomidate; nerve, neurotransmitters, GABA

Subjects aged 75 yr or more represent a growing subpopulation of surgical patients. The perioperative management of these patients has to deal with physiological, pharmacological and psychological changes associated with aging, which represent risk factors for concomitant disease and death.[1] Several lines of evidence suggest that aging may induce alterations in the pharmacodynamics of anaesthetic agents in the CNS. Indeed, sensitivity to the hypnotic effects of midazolam is increased in elderly surgical patients, independent of pharmacokinetic phenomena.[2] Also, the alteration of psychomotor functions observed at emergence from propofol anaesthesia in surgical patients aged 70 or more is likely to be mediated in part via pharmacodynamic mechanisms.[3] We have recently shown that some i.v. anaesthetics inhibit the reuptake of GABA in a reversible fashion *in vitro*.[4] This might contribute to the production of unconsciousness *in vivo*. Therefore, in the present study, we have examined the effect of aging on the sensitivity of the GABA carrier to etomidate and propofol in a preparation of striatal synaptosomes (pinched-off nerve endings) *in vitro*.

Methods and results

Handling procedures, as written in the Guide for the Care and Use of Laboratory Animals, were followed throughout. Experiments were performed on male Sprague–Dawley rats (Iffa-Credo, France) aged 2, 18 and 24 months housed on a 12-h light–dark cycle with food and water *ad libitum*. Animals were killed by stunning and decapitation, and striata quickly removed from the brains and placed into ice-cold sucrose 0.32 mol $litre^{-1}$ containing EDTA 1 mmol $litre^{-1}$, dithiothreitol 0.25 mmol $litre^{-1}$ and adjusted to pH 7.4. Synaptosomes were isolated and purified on a four-step Percoll gradient and diluted to protein of 0.16 mg ml^{-1} with artificial cerebrospinal fluid (CSF) at 4 °C. The composition of the CSF was, in mmol $litre^{-1}$: NaCl 126.5; $NaHCO_3$ 27.5; KCl 2.4; KH_2PO_4 0.5; $CaCl_2$ 1.1; $MgCl_2$ 0.83; Na_2SO_4 0.5; glucose 11.8; aminooxyacetic acid an inhibitor of GABA catabolism, (Sigma, France) 0.1 and β-alanine (an inhibitor of the GABA carrier in glial cells, Calbiochem, USA) 1; the pH was adjusted to 7.3 with a 95:5 v/v oxygen–carbon dioxide mixture.

Uptake was initiated by adding $[2,3\ ^3H]$-GABA (Amersham, UK, 60 $Ci.mmol^{-1}$, 20 nM) to the synaptosomal suspension at 37 °C. This was performed in either the absence of any pharmacological or anaesthetic agent (control), or both, or the presence of nipecotic acid (a specific competitive inhibitor of neuronal GABA uptake), etomidate and propofol (10^{-6}–10^{-3} mol $litre^{-1}$). Etomidate and propofol were dissolved in dimethylsulphoxide (Merck, Germany). After 5-min incubation, the mixture was vacuum filtered through glass filters (Whatman, GF/F, 0.70-μm retention capacity) and washed with 10 ml of ice-cold CSF. The radioactivity retained on the filters was extracted with NaOH 0.1 mol $litre^{-1}$ and measured by liquid scintillation in Aquasol 2 (New England Nuclear, USA). Specific $[^3H]$-GABA uptake was defined by the difference between the radioactivity measured in both the presence and absence of nipecotic acid (10^{-3} mol $litre^{-1}$).

The kinetics of anaesthetic-induced inhibition of $[^3H]$-GABA uptake were investigated in 2-month-old rats by incubating synaptosomes (37 °C, 5 min) with increasing concentrations of $[^3H]$-GABA (20–200 nmol $litre^{-1}$) as previously reported.[4] The reaction was stopped by addition of ice-cold CSF followed by vacuum filtration, and the radioactivity retained on the filters measured. Kinetic variables of the reaction (maximum velocity, Vmax; Michaelis-Menton constant, K_m) were determined by genera-

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tion of double reciprocal plots in the absence (control) and presence of a fixed concentration of anaesthetic corresponding to the IC$_{50}$ value.

Concentration-response curves were generated by computer and IC$_{50}$ values for inhibition of [^{3}H]-GABA uptake calculated using the GraphPAD software (USA). Results were considered reliable only if they had been reproduced in at least four independent experiments (each of them run in triplicate). Statistical comparison of the IC$_{50}$ values in 2-, 18- and 24-month-old rats was performed by the Kruskal–Wallis test followed by the Mann–Whitney *U* test. $P<0.05$ was considered the threshold for significance.

Synaptosomal [^{3}H]-GABA uptake increased linearly with time and protein concentration. Mean value was 0.90 (SD 0.07) pmol litre^{-1} mg protein^{-1} after 5-min incubation.[4] Non-specific uptake was always less than 5% of the total filter retained radioactivity.

Nipecotic acid, etomidate and propofol induced a concentration-related inhibition of [^{3}H]-GABA uptake. In the 2-month-old animals, IC$_{50}$ values were mean 3.6 (SD 0.3), 46 (3) and 58 (3) µmol litre^{-1} for nipecotic acid, propofol and etomidate, respectively. Dimethylsulphoxide did not affect [^{3}H]-GABA uptake. Etomidate and propofol inhibition was non-competitive in that the K$_m$ remained constant but there was a significant decrease in Vmax observed between control experiments and those containing these anaesthetics: V max (pmol mg protein^{-1} 3 min^{-1}) = 30 (4.1) for control and 22 (2.6) and 21.3 (3.3), $P<0.05$, for propofol and etomidate, respectively; K$_m$ (µmol litre^{-1}) = 6.2 (0.7) for control, and 5.4 (0.9) and 5.8 (0.8) for propofol and etomidate, respectively.

The influence of aging on the inhibition by anaesthetics of [^{3}H]-GABA uptake is displayed in table 1.

There was a significant increase in the values for IC$_{50}$ of both propofol and etomidate in the 24-month-old rats. This value was found significantly increased for propofol, but not etomidate, in the 18-month-old animals. No significant change in the inhibitory effect of nipecotic acid was observed whichever the subpopulation of rats examined.

Comment

This study shows for the first time that aging induces functional alterations of neurotransmitters relevant to anaesthesia and subsequently produces changes in the pharmacodynamics of anaesthetics in the CNS. Indeed, the sensitivity of the GABA carrier to propofol and etomidate, two agents currently used, is decreased in old compared with young rats, as assessed by a significant increase in the IC$_{50}$ values for propofol (at 18 and 24 months) and etomidate (at 24 months). The IC$_{50}$ values reported here for the inhibition of GABA uptake by nipecotic acid, propofol and etomidate and the kinetic analysis of this inhibition are consistent with our previous results.[4] These anaesthetic concentrations are slightly greater than those required to produce anaesthesia.[5] However, they can be considered clinically relevant, because they are in the range of those found in the plasma of anaesthetized humans.[6 7] Therefore, the present data confirm and extend the observation that propofol and etomidate inhibit the activity of the GABA carrier in a non-competitive fashion.

Table 1 Influence of aging on the inhibition of [^{3}H]-GABA uptake by anaesthetics (mean (SD)). ** $p<0.01$, ***$p<0.001$ *vs* 2 months. *n* refers to the number of independent experiments.

Age (months)	IC$_{50}$ values (µmol litre^{-1})		
	Nipecotic acid	Propofol	Etomidate
2 (*n*=6)	3.6 ± (0.3)	46 ± (3)	58 ± (0.8)
18 (*n*=6)	5.6 ± (0 8)	225 ± (21)***	44 ± (4)
24 (*n*=6)	3.9 ± (0.7)	161 ± (16)***	149 ± (14)**

The mechanisms underlying the aging-related decrease in sensitivity to propofol and etomidate remain to be elucidated. An aging-related neuronal loss has been reported in some species, but the functional relevance of this phenomenon remains controversial.[8] Whether anaesthetics interact via the lipid environment of the GABA carrier or directly with the protein cannot be inferred from our data. Interestingly, and in contrast with propofol and etomidate, the potency of nipecotic acid to block GABA uptake was not affected by aging. Therefore, it is likely that propofol and etomidate do not share the same mechanism for blocking GABA uptake as nipecotic acid, and that aging selectively affects the anaesthetic-carrier interaction.

A major consequence of blocking GABA uptake is to increase the background levels of GABA activating extrasynaptic GABA$_A$ or even GABA$_B$-mediated synaptic transmission. This may contribute to the production of the anaesthetic state. The clinical relevance of the aging-related decrease in sensitivity to propofol and etomidate of the GABA carrier remains to be determined. It can be speculated that these or other related pharmacodynamic changes might contribute to the modifications in anaesthetic requirements that are observed in the elderly.

Acknowledgement

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Duration of the pharmacodynamic interaction between pancuronium and mivacurium

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Summary

The aim of this study was to determine for how long the duration of action of increments of mivacurium can be influenced by previous pancuronium administration. Fifteen patients, ASA I or II, undergoing general anaesthesia for major abdominal surgery were investigated. The post-tetanic count (PTC) was measured at the adductor pollicis muscle. Pancuronium 0.1 mg kg^{-1} was injected first. At recovery of the 10th response of the PTC (PTC10), a second dose of pancuronium was injected (0.02 mg kg^{-1}). On recovery to PTC10, a bolus of mivacurium (0.04 mg kg^{-1}) was given and regularly repeated at recovery of PTC10 until the end of surgery. The mean duration of the second dose of pancuronium was 53 min (SD 13 min) and of the first dose of mivacurium, 66 min (SD 14 min) (P<0.01). The duration of action of further mivacurium boluses decreased significantly until the fifth dose. It took 222 minutes (95% confidence interval 190, 253 min) after the second pancuronium dose before the duration of action of mivacurium returned to normal values and became constant and predictable. (*Br. J. Anaesth.* 1998; **81**: 251–252)

Keywords: antagonists; neuromuscular block, pancuronium; neuromuscular block, mivacurium; recovery

Long-acting neuromuscular blocking drugs are often used during major abdominal surgery to provide adequate surgical conditions throughout the procedure. Such practice leads to a high incidence of residual neuromuscular block in the recovery room.[1] To avoid this adverse effect, some anaesthetists use short-acting agents for closure of the abdominal wall after previous administration of long-acting neuromuscular blocking drugs, and expect a faster recovery from neuromuscular block at the end of surgery. However, when using more than one non-depolarizing neuromuscular blocking drug, unpredictable pharmacodynamic interactions may occur. Indeed, a significant prolongation of action of mivacurium has already been shown after previous administration of pancuronium.[2 3] The purpose of the previous studies was to demonstrate supra-additive effects during concomitant administration of two neuromuscular blocking agents. A single dose of mivacurium and pancuronium was given. However, the duration of the interaction between the two neuromuscular blocking drugs remains unknown. Pharmacokinetic data and concentration-response relations suggests that such interaction could possibly last many hours: pancuronium remains in the biophase for a long time.[4] The aim of the study was to determine for how long the duration of action of mivacurium can be influenced by previous pancuronium administration.

Methods and results

Fifteen patients, ASA I or II, scheduled for prolonged major abdominal procedures were studied. This investigation was approved by the local ethics committee. Exclusion criteria were the presence of neuromuscular, hepatic or renal disease, and concurrent administration of any drugs known or suspected to interfere with neuromuscular transmission.

Anaesthesia was induced with propofol (2–3 mg kg^{-1}) and fentanyl (2–3 μg kg^{-1}). After induction, supramaximal transcutaneous train-of-four stimulation (TOF) at the ulnar nerve was applied. Responses were measured on the adductor of the thumb with an accelerometer (Tof-Guard, Organon, Teknika NV, Belgium). After calibration, pancuronium (0.1 mg kg^{-1}) was administered and tracheal intubation was performed. Anaesthesia was maintained with a continuous infusion of propofol and incremental bolus doses of fentanyl at the discretion of the anaesthetist. End-tidal concentrations of carbon dioxide were kept constant within 4–4.5% (Capnomac, Datex, Helsinski, Finland). Intraoperative hypothermia was prevented with forced air-warming blankets (Bair Hugger, Augustine Medicale, Minneapolis, USA) covering the upper part of the body and forearms of the patient, without interfering with thumb mobility.

When the response to TOF stimulation disappeared after pancuronium administration, the post-tetanic count (PTC) was measured every 5 min (50 Hz tetanus for 5 s followed 3 s later by single twitch stimulation at 1 Hz). At the time of reappearance of the tenth response of the PTC (PTC10), a bolus of pancuronium 0.02 mg kg^{-1} was given. Recovery of the PTC10 was again awaited before an approximately equipotent dose of mivacurium (0.04 mg kg^{-1}) was given. Further boluses of mivacurium (0.04 mg kg^{-1}) were again given at the same depth of neuromuscular block (PTC10) until the end of the procedure.

The time to recovery of the PTC10 after each injection of neuromuscular blocking drug, and the interval between the second pancuronium dose and the time when the duration of action of two consecutive mivacurium doses did not differ significantly, were recorded for each patient.

The Wilcoxon paired-sample test (StatView 4–5, Abacus Concepts Inc, Berkeley, USA) was used for statistical analysis. A P value of 0.05 or less was considered statistically significant. Results are expressed

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as mean (SD) unless otherwise stated. The physical characteristics of the population (9 females and 6 males) were 55 years (range 40–63) and 63 (14) kg. The mean duration of anaesthesia was 323 min (range = 160 to 494 min). Every injection of pancuronium and mivacurium abolished the PTC response. The mean time from first injection of pancuronium until reappearance of the PTC10 was 55 (15) min. The duration of action of the first injection of mivacurium was 66 (14) min, exceeding significantly the duration of action of the second dose of pancuronium (53 (13) min, $P<0.01$).

The duration of action of the incremental doses of mivacurium decreased progressively with time (fig. 1). The time between two consecutive mivacurium doses did not differ significantly after the fifth increment, corresponding to a mean of 222 minutes after the last pancuronium injection (95% confidence interval 190, 253 min).

Core intraoperative hypothermia did not occur in any patient.

Comment

The duration of the pharmacodynamic interaction between pancuronium and mivacurium has never been investigated. We found that the duration of action of repeated mivacurium bolus doses returned to a constant and predictable level approximately 4 h after the last pancuronium administration.

The first part of our findings corroborates previous studies showing prolongation of the duration of action of mivacurium when administrated after pancuronium.[2 3] We found that after pancuronium administration, the duration of action of mivacurium was significantly longer than the duration of action of approximately equipotent doses of pancuronium. The ED_{95} for pancuronium is wide ranging (0.05–0.07 mg kg^{-1}) and we probably used a slightly underestimated value. However, Erkola and colleagues showed that large differences in the size of the administrated doses of mivacurium after pancuronium administration did not have a great effect on the magnitude of the pharmacodynamic interaction between the two drugs.[2] Moreover, the ED_{95} refers especially to the post-synaptic activity of non-depolarizing neuromuscular blocking drugs but the potentiating effect of different agents may be related at least in part to differences in presynaptic activity.[5] Furthermore, presynaptic mechanisms are also involved in the response to tetanic stimulation. The longer depression of the PTC stimulation we observed after mivacurium could reflect a greater degree of presynaptic inhibition than with pancuronium alone.

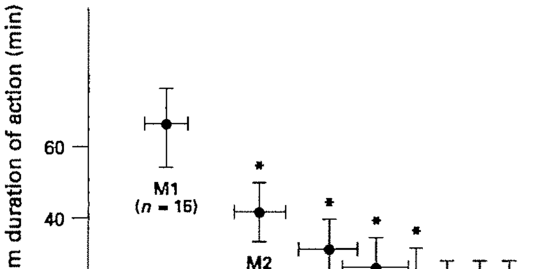

Figure 1 Duration of action of mivacurium increments (M1–M8) after the second pancuronium dose (P). Vertical lines represents SD of the duration of action of the bolus dose of mivacurium. Horizontal lines represent the SD of the time to injection of the mivacurium dose. Number of patients are given in parentheses under the bolus number. * Duration of action significantly different from the previous injection ($P<0.05$).

It took nearly 4 h for the duration of action of mivacurium to become stable. It is a minimum value, as the probability of failing to find a difference in duration between two consecutive mivacurium boluses when there really is one (type II error) is high because of the small sample size.

Pancuronium is a long-acting neuromuscular blocking drug which remains at the neuromuscular junction for an extended period. The clinical effect of pancuronium in healthy subjects is known to last over 90–120 min.[4] When recovery from neuromuscular block occurs, pancuronium is still present in the synaptic cleft.[6] The rate of elimination of residual pancuronium from the biophase is affected by the plasma concentration of pancuronium. In healthy subjects, the elimination half-life of pancuronium have been found to be around 110 min.[7] Thus it can be expected that the post-synaptic receptors remain occupied by pancuronium for many hours after a bolus of the drug. In the circumstances of this study, the prolongation of action of repeated doses of mivacurium suggests residual occupation of acetylcholine receptors by pancuronium. The magnitude of the prolongation of the duration of action of mivacurium decreases concomitantly with time from the last pancuronium injection, probably in a similar manner to the fall in the residual concentration of pancuronium in the biophase.

In conclusion, clinicians must be aware that the duration of action of mivacurium is altered for a mean of approximately 4 h after a dose of pancuronium. Thus, substitution of pancuronium with mivacurium for abdominal wall closure at the end of prolonged surgery is inadvisable. It seems preferable to administer mivacurium by continuous infusion throughout the operation, thus providing a more easily controlled neuromuscular block with a predictable rate of recovery when the infusion is terminated.

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Effects of lightwand (Trachlight) compared with direct laryngoscopy on circulatory responses to tracheal intubation

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Summary

We compared the effects of the lightwand technique on circulatory responses to tracheal intubation with those of direct-vision laryngoscopy. Forty adult patients received propofol and vecuronium, and their lungs were ventilated for 2 min via a mask with 5% sevoflurane in oxygen, after which the trachea was intubated orally using either the lightwand (Trachlight, *n*=20) or the Macintosh laryngoscope (*n*=20). Maximum mean arterial pressure changes did not differ between groups during (lightwand group, 25 (SD 21) mm Hg *vs* laryngoscopy group, 23 (19) mm Hg) and after (21 (24) mm Hg *vs* 21 (16) mm Hg) tracheal intubation. Maximum heart rate changes were similar for groups during (16 (14) beat min^{-1} *vs* 16 (15) beat min^{-1}) and after (2 (11) beat min^{-1} *vs* 7 (19) beat min^{-1}) tracheal intubation. There were no differences between the lightwand technique and direct-vision laryngoscopy in changes in mean arterial pressure and heart rate during and after tracheal intubation. We conclude that the effects of the lightwand technique on circulatory responses to tracheal intubation were similar to those of direct-vision laryngoscopy. (*Br. J. Anaesth.* 1998; **81**: 253–255)

Keywords: intubation, tracheal; anaesthetic techniques, lightwand; anaesthetic techniques, laryngoscopy

Tracheal intubation by direct vision using a laryngoscope after rapid sequence induction of anaesthesia is frequently associated with circulatory changes.[1-4] The circulatory changes occur in response to the stimuli of both direct-vision laryngoscopy and placement of the tube in the trachea. In particular, the circulatory changes are severe when the duration of direct-vision laryngoscopy is prolonged.[5] In contrast, transillumination of the soft tissue of the neck using a lightwand (Trachlight, Laerdal Medical, Armonk, NY, USA) is a gentle intubating technique in which no direct-vision laryngoscopy is required.[6-8] We therefore hypothesized that this gentle intubating technique using the Trachlight would be associated with less circulatory changes compared with the standard technique using direct-vision laryngoscopy. The aim of this study was to compare the effects of lightwand technique on circulatory responses to tracheal intubation with those of direct-vision laryngoscopy.

Methods and results

The study was approved by the Hospital Ethics Committee and informed consent was obtained from 40 patients, ASA I or II, undergoing elective (abdominal, orthopaedic, or otorhinological) surgery. Patients with hypertension, cardiovascular disease or arteriosclerotic disease were excluded from the study. Preanaesthetic medication consisted of atropine (0.5 mg) and hydroxyzine (50 mg) i.m. Upon arrival in the operating room patients were monitored with ECG lead II for measuring heart rate, and an 18-gauge i.v. catheter was inserted in an upper extremity vein. A local anaesthetic (1% mepivacaine) was injected intradermally with a 26-gauge needle, and a 22-gauge catheter was inserted in a radial artery to permit continuous recording of systolic and diastolic arterial pressures. Anaesthesia was induced with a propofol solution (0.2 ml kg^{-1}), which consisted of propofol 180 mg and lidocaine 40 mg in a total volume of 20 ml, followed by vecuronium (0.1 mg kg^{-1}). The lungs of all the patients were ventilated for 2 min via a mask with 5% sevoflurane in oxygen, and then the trachea was intubated orally using either the lightwand (Trachlight, *n*=20) or the Macintosh laryngoscope (*n*=20). The allocation to the two groups was randomly performed using sealed envelopes but not blinded to the investigator. Anaesthesia was maintained with 3% sevoflurane and 66% nitrous oxide in oxygen for 3 min. After the study period, the anaesthetics used were not standardized. Arterial pressure and heart rate were recorded at the following times: (A) before anaesthesia induction, (B) 2 min after anaesthesia induction before tracheal intubation, (C) when the trachea was just intubated, (D) maximum increase after tracheal intubation, (E) 1 min after tracheal intubation, (F) 2 min after tracheal intubation, and (G) 3 min after tracheal intubation. The time necessary to place a tracheal tube and the time of maximum increase in arterial pressure after tracheal intubation was measured by a stopwatch.

Statistical analyses were performed with the StatView SE package (Abacus Concepts, CA, USA) on a Power Macintosh 7200 (Apple Computer Inc., CA, USA). Patient characteristics were compared

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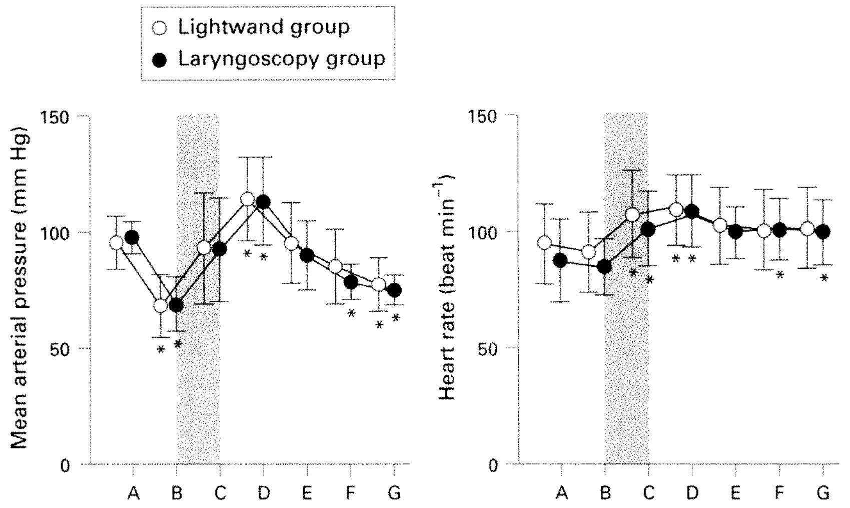

Figure 1 Mean arterial pressure (left panel) and heart rate (right panel) in the lightwand (open symbols) and laryngoscopy (closed symbols) groups. A: before anaesthesia induction; B: 2 min after anaesthesia induction before tracheal intubation; C: when the trachea was just intubated; D: maximum increase after tracheal intubation (23 (12) s after tracheal intubation in the lightwand group and 23 (9) s in the laryngoscopy group); E: 1 min after tracheal intubation; F: 2 min after tracheal intubation; and G: 3 min after tracheal intubation. The shaded area indicates the duration of the lightwand technique (22 (11) s) or laryngoscopy (24 (11) s). *$P<0.05$ compared with before anaesthesia induction. No significant differences were found between the two groups in changes in mean arterial pressure and heart rate.

using Student's *t* test. Within group changes over time were analysed with analysis of variance (ANOVA) for repeated measures. Between group differences were compared using ANOVA for factors. If significant differences were observed, Scheffe *F* was used for *post hoc* analysis. Data are presented as mean (SD). $P<0.05$ was considered statistically significant.

Patients in the two groups were comparable in age (lightwand group, 44 (22–69) yr *vs* laryngoscopy group, 40 (22–77) yr), weight (58 (12) kg *vs* 55 (9) kg) and height (159 (8) cm *vs* 161 (9) cm). The time necessary to place a tracheal tube did not differ between groups (22 (11) s *vs* 24 (11) s).

After anaesthesia induction, mean arterial pressure decreased to a similar extent in both groups ($P<0.05$, fig. 1). The increase in mean arterial pressure during tracheal intubation did not differ between the groups (25 (21) mm Hg *vs* 23 (19) mm Hg), and an additional increase in mean arterial pressure after tracheal intubation was not different between the groups (21 (24) mm Hg *vs* 21 (16) mm Hg). The time of maximum increase in mean arterial pressure after tracheal intubation did not differ between the groups (23 (12) s *vs* 23 (9) s). In both the groups, maximum mean arterial pressure after tracheal intubation was significantly greater ($P<0.05$), from the preanaesthetic values, and this decreased within 1 min. No significant differences in mean arterial pressure changes were found between the groups at any time.

Heart rate after anaesthesia induction did not differ between the groups (fig. 1). The increase in heart rate during tracheal intubation was not different between groups (16 (14) beat min^{-1} *vs* 16 (15) beat min^{-1}). In both groups, heart rate after tracheal intubation was significantly greater ($P<0.05$), compared with the preanaesthetic values. The increase in heart rate after tracheal intubation did not differ between groups (2 (11) beat min^{-1} *vs* 7 (19) beat min^{-1}). There were no significant differences in heart rate changes at any time between the groups.

Comments

Orotracheal intubation using the direct-vision laryngoscopy requires elevation of the epiglottis and exposure of the glottic opening. The elevation of the epiglottis and exposure of the glottis opening is obtained by a forward and upward movement of the laryngoscope blade exerted along the axis of the laryngoscope handle, and may result in circulatory responses. In contrast with direct-vision laryngoscopy, the lightwand method of intubation requires neither elevation of the epiglottis by the laryngoscope blade nor exposure of the glottic opening. We predicted that this gentle technique would cause less circulatory changes than standard direct-vision laryngoscopy. In contrast with our expectation, we found that the circulatory responses to tracheal intubation were similar to those of direct-vision laryngoscopy.

Both mean arterial pressure and heart rate increased significantly in our laryngoscopy group. These may reflect the stimulus of the areas being in contact with the laryngoscopy blade. In the lightwand group we also found the significant circulatory changes which were comparable to the laryngoscopy group. In the technique for lightwand intubation, the jaw is grasped and lifted upward using the thumb and index finger of the intubator's hand. This lifts the tongue and epiglottis off the posterior pharyngeal wall to make a clear passage for the tracheal tube to enter the glottic opening.[7] This manoeuvre seems to be gentle compared with the direct-vision laryngoscopy. The results of the present study, however, suggest that the magnitude of this stimulus was sufficient to cause circulatory responses.

When the tracheal tube was placed, an additional increase in mean arterial pressure was found in both the groups. Maximum pressure response to direct-vision laryngoscopy has been reported by 45 s.[5] In the present study the time necessary to place a tracheal tube was 22 (11) s in the lightwand group and 24 (11) s in the laryngoscopy group, so maximum pressure responses might not have taken place and the placement of the tracheal tube would hence result in the additional increase in mean arterial pressure after tracheal intubation.

None of the patients examined in this study had hypertension, cardiovascular disease or arteriosclerotic disease. Reduction of pressure responses to tracheal intubation might be important in such patients. Investigations of the lightwand technique on circulatory responses to tracheal intubation in such patients would be of interest.

Finally, in the current study atropine was applied during premedication. Atropine may alter circulatory responses to tracheal intubation. However, because all patients received atropine for premedication, the comparison of these two groups is valid.

In summary, this study has shown that there were no differences between the lightwand technique and direct-vision laryngoscopy in the changes in mean arterial pressure and heart rate during and after tracheal intubation. We conclude that the effects of lightwand technique on circulatory responses to tracheal intubation were similar to those of direct-vision laryngoscopy.

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British Journal of Anaesthesia 1998; **81**: 256–259

CASE REPORTS

Perioperative care of a Jehovah's Witness with a leaking abdominal aortic aneurysm

C. E. BAKER, G. D. KELLY AND G. D. PERKINS

Summary

We describe a Jehovah's Witness patient who survived emergency repair of a leaking abdominal aortic aneurysm. In accordance with his beliefs, the patient expressed a wish not to be given blood and this was respected. At completion of surgery, his haemoglobin was 2.8 g dl^{-1} and his albumin was 8 g l^{-1}. He was kept heavily sedated in the intensive care unit and treated with i.v. iron, folinic acid and s.c. epoetin alfa. He was discharged to the high dependency unit 18 days after surgery with a haemoglobin of 6.4 g dl^{-1} and an albumin of 27 g l^{-1}. After rehabilitation, he was discharged home approximately 14 weeks after surgery. (*Br. J. Anaesth* 1998; **81**: 256–259)

Keywords: surgery, abdominal aortic aneurysm; religion, Jehovah's Witness; blood, refusal; epoetin alfa; ferric hydroxide sucrose

There are currently about 130 000 Jehovah's Witnesses in the United Kingdom. Their beliefs do not permit them to receive whole blood or packed cells. The use of other blood products or cell salvage techniques may be allowable. For an elective procedure, guidance for both doctors and patients can be sought from the Jehovah's Witness hospital liaison committee. Ultimately, the decision to accept or refuse blood or blood products rests upon the conscience of each individual member.

Case report

A 67-year-old Afro-Caribbean male who was a Jehovah's Witness collapsed in the street and was brought to the emergency department in a shocked state with a systolic arterial pressure of 80 mm Hg, a tachycardia of 120 beats per minute and poor peripheral perfusion. A clinical diagnosis of a leaking abdominal aortic aneurysm was made. An ultrasound scan confirmed the diagnosis; it revealed a fusiform dilatation of an infra-renal aneurysm with signs of acute haemorrhage and a large retro-peritoneal haematoma. The patient received gelatin (Gelofusine) 1.5 litres before transfer to the operating theatre.

On arrival in the operating theatre, the patient was alert and orientated. The risks and benefits of the procedure and the particular risk inherent in refusing blood were explained to the patient. Fully understanding the implications of his decision, the patient reaffirmed his beliefs and asked that he not be transfused with blood. The patient was aware of the possibility of cell salvage but it was not available at the hospital.

The patient was transferred to the operating table, intra-arterial monitoring was commenced, a urinary catheter was inserted and the patient was prepared for surgery. The patient was pre-oxygenated and cricoid pressure applied. Anaesthesia was induced with fentanyl 250 μg, thiopental sodium 150 mg and succinylcholine 100 mg. The trachea was intubated and anaesthesia was maintained with isoflurane in oxygen (50%) and nitrous oxide. Further neuromuscular block was obtained using rocuronium bromide. Central venous access was obtained peroperatively with a triple lumen catheter and a "Swan sheath" introducer. During the operation, the patient received hetastarch (Hespan) 1.5 litres, Hartmann's solution 1 litre, saline 0.9% 4 litres, and mannitol 10% 500 ml. Intra-operative blood loss into the suction jars was 1.6 litres.

The aorta was clamped within 5 min of commencement of surgery. A straight 20-mm graft was sutured in place. The aortic clamp time was 55 min and the total duration of surgery was 2 h and 10 min. During the operation decreases in the patient's arterial pressure initially responded to fluid boluses. When this was no longer the case despite a central venous pressure (CVP) of 18–20 mm Hg, a norepinephrine infusion was prepared. Meanwhile a bolus of epinephrine 50 μg was given which, in addition to raising the arterial pressure, gave rise to a tachycardia and marked ST segment depression on the ECG; this gradually resolved over the subsequent 10 min. The norepinephrine infusion restored the arterial pressure to an acceptable level. It was continued in the intensive care unit (ICU), initially at a rate of 0.07 μg kg^{-1} min^{-1} and increased to 0.24 μg kg^{-1} min^{-1} during the first postoperative night. A good urine output was maintained throughout the duration of surgery.

On arrival in the ICU, the patient was kept heavily sedated with morphine and propofol 1% and the lungs artificially ventilated. Midazolam was substituted for propofol the next day in view of the anticipated long ICU stay. No neuromuscular blocking drugs were required to facilitate ventilation. Total

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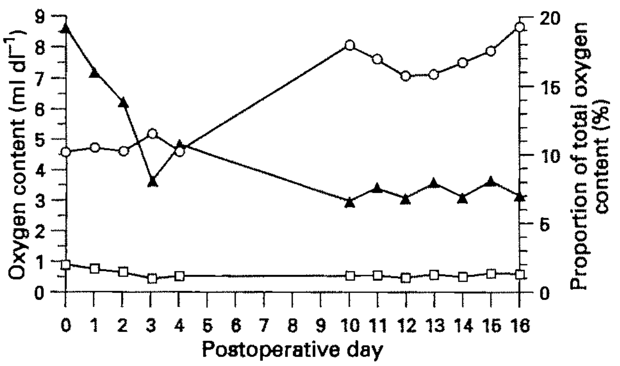

Figure 1 Comparison of total and dissolved oxygen content during the first 16 postoperative days. Symbols represent total arterial oxygen content (open circles), actual dissolved oxygen content (open squares) and dissolved oxygen content as a percentage of total oxygen content (solid triangles). No blood samples were taken from days 5–9.

parenteral nutrition (TPN), i.v. iron, folinic acid 15 mg per day and s.c. epoetin alfa 1000 units per day were started immediately in an attempt to maximally stimulate the bone marrow and provide the optimal conditions for haemopoiesis. Vitamin K 10 mg three times a day was given i.v. to promote production of coagulation factors.

The patient's axillary temperature was 34 °C on admission to the ICU. A decision was taken not to rewarm the patient actively as this may have increased tissue oxygen requirements, nor was he actively cooled as this may have exacerbated any coagulopathy.[1,2] The F_{IO_2} was maintained at 0.6 for the duration of his ICU stay to increase oxygen delivery to the tissues whilst minimizing the risk of oxygen toxicity to the lungs.[3] Although the dissolved oxygen content remained fairly constant, it initially contributed up to 19% of the total oxygen transported in the blood (fig. 1).

Blood tests were kept to a minimum; no blood was taken at all on the fifth to ninth postoperative days and blood was sent in bottles used in paediatric practice whenever possible. Haemoglobin on admission to the ICU was 2.8 g dl^{-1} on the blood-gas machine (Radiometer ABL 510) and 3.0 g dl^{-1} in the laboratory. The plasma albumin was 8 g litre^{-1}. The international normalized ratio (INR) was 2.9 and the partial thromboplastin time (PTT) was 63 s (normal range 27–37 s). The INR was normal by day 5 and the APTT and platelet count were within normal range by day 10. Daily coagulation checks were not performed as we had no therapeutic intervention to offer and the patient showed no signs of active haemorrhage.

Lactate concentrations (Radiometer EML 105) were normal by 10 h postoperatively and the standard base excess was within normal limits by 72 h.

Considerable thought was given as to whether or not to insert a pulmonary artery catheter to assist in fluid and inotrope management. In the hours immediately after the operation, the patient had occasional ventricular ectopics, but arterial pressure was not compromised. In view of the patient's adequate arterial pressure, acceptable urine output, improving acid-base balance (fig. 2) and dependence on a low dose of just one inotrope, we could not clinically justify the use of a pulmonary artery catheter, although we appreciated that the data obtained would have been useful. We therefore relied on CVP readings to guide fluid requirements and tried to maintain the right heart filling pressure at 12–14 mm Hg. This was achieved in the first 48 h postoperatively with additional crystalloid 2.5 litres, Gelofusine 1 litre, Hespan 1.5 litres and the maintenance fluid provided by the TPN. Clinically, there was no overt evidence of left or right heart failure.

By the fourth postoperative day, the norepinephrine had been discontinued and enteral feeding had commenced. The patient maintained a good diuresis and towards the end of his stay in the ICU, his cumulative fluid balance became slightly negative (fig. 3).

By the 10th day, there was some green sputum on tracheal aspiration. This was sent as part of our weekly multi-resistant staphylococcus aureus (MRSA) screening programme. Gram staining revealed Gram positive staphylococci which were initially treated

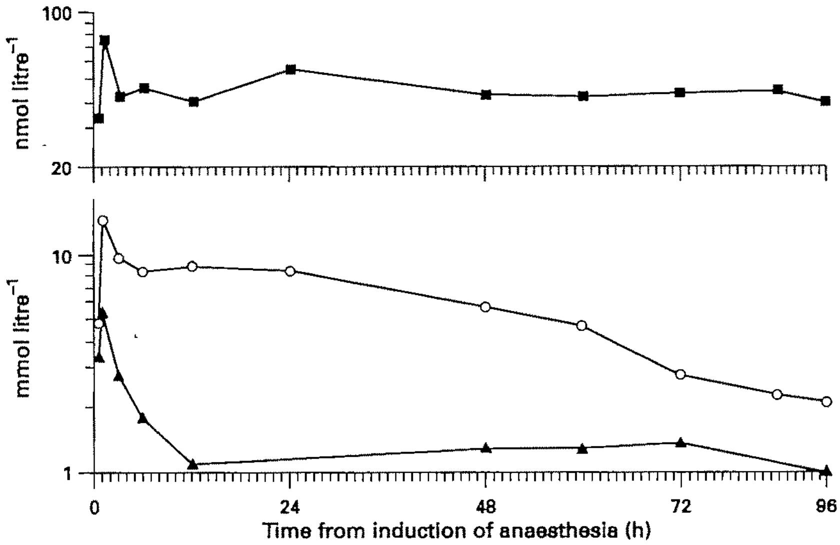

Figure 2 Changes in markers of tissue oxygenation over the first four postoperative days. Symbols represent hydrogen ions (solid squares), standard base deficit (open circles) and lactate (solid triangles).

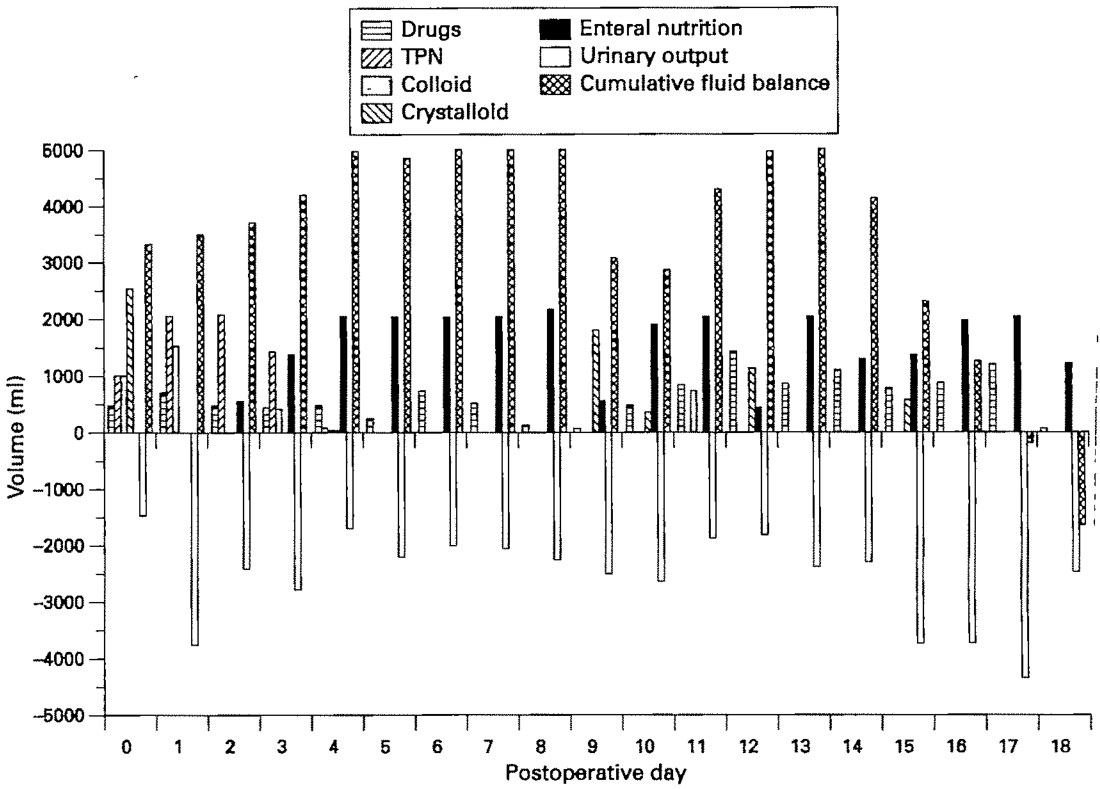

Figure 3 Fluid balance for the duration of stay in the intensive care unit. Drugs include sedation, analgesia, norepinephrine, antibiotics, i.v. iron, folinic acid and epoetin alfa.

with ciprofloxacin and vancomycin. Two days later, the organism was identified as MRSA and the antibiotics were changed, according to drug sensitivities, to rifampicin and gentamicin. There was no clinical or radiological evidence of pneumonia, however.

On the 12th day, a surgical tracheostomy was performed because of gross glossal oedema caused by tongue biting. The patient was weaned from full artificial ventilation to continuous positive airway pressure (CPAP) and positive pressure support, without difficulty on the 14th postoperative day. Three days later the patient was breathing spontaneously on a "T piece". The following day the tracheostomy tube was changed to a size 6.0-mm non-cuffed tube before transfer of the patient to the high dependency unit (HDU). Two weeks later, the uncuffed tube was substituted for a mini-tracheostomy and the trachea was finally decannulated one week later.

A blood film and reticulocyte count performed on the 15th day reported "basophilic stippling and polychromasia", suggesting accelerated erythropoiesis and the presence of a young red cell population. The reticulocytes represented 3.5% of the red cell count, the normal value being approximately 1%. The day before discharge to the HDU the haemoglobin was 6.4 g dl^{-1} and the albumin was 27 g l^{-1} (fig. 4). The patient was discharged to a rehabilitation ward eight weeks after admission to hospital. After six weeks of rehabilitation the patient was independent and finally discharged back to his own home, 14 weeks after admission.

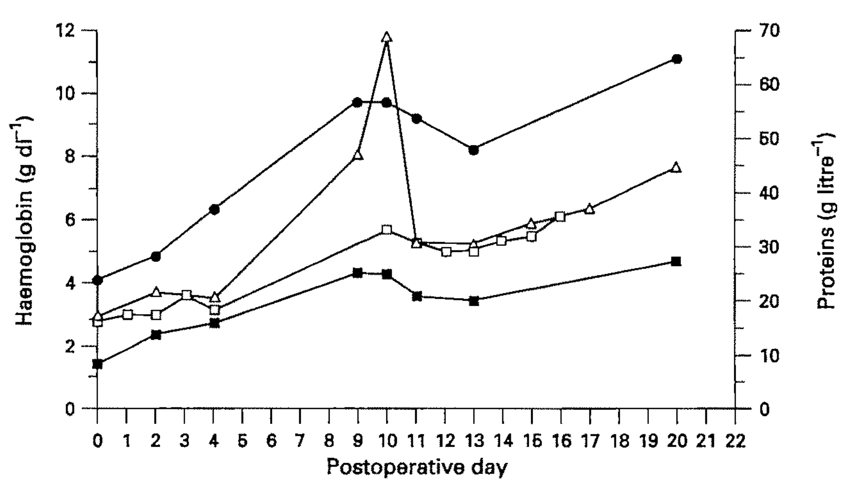

Figure 4 Changes in haemoglobin, albumin and total protein during the first 22 postoperative days Symbols represent laboratory-measured haemoglobin (open triangle), haemoglobin measured using the blood-gas analyser (open squares), total protein (solid circles) and albumin (solid squares). No blood samples were taken from days 5–9.

Discussion

We believe that this is the first reported case of a Jehovah's Witness surviving an emergency abdominal aortic aneurysm repair. This patient's initial survival depended on his resuscitation, his physiological responses to the insult he received and the surgical team. As this was an emergency procedure, it was not possible to inquire in detail preoperatively if any blood products may have been acceptable to the patient. As a consequence, the patient may well have endured a more rigorous blood product exclusion policy than his conscience would have allowed.

To provide substrates for haemoglobin synthesis and to stimulate its production we used TPN, i.v. iron, folinic acid and s.c. epoetin alfa. We initially prescribed two litres of a proprietary parenteral feed providing nitrogen 14 g and 1590 kcal over 24 h. The hospital TPN team reviewed the patient and produced a formulation providing nitrogen 11.4 g and 2000 kcal per day in approximately two litres. By the fourth day, enteral feeding was established with proprietary enteral feed and TPN was discontinued.

There is currently no licensed i.v. iron preparation in the United Kingdom. The patient's iron deficit was estimated to be in the order of 1400–2300 mg. We gave i.v. iron saccharate (Venofer) 1600 mg, over the duration of the ICU stay. Venofer contains 100 mg of trivalent iron in each ampoule and has been available in the United Kingdom for the last three years on a named patient basis only. We gave epoetin alfa 1000 units per day, but we later became aware that this does contain a small amount of human albumin. A more suitable product may have been epoetin beta as this is free of human albumin. We had two unexpectedly high haemoglobin results from the laboratory that did not correlate with the general trend or the haemoglobin level from the blood-gas machine; we are unable to account for these aberrant values.

In acute haemodilution, oxygen transport and tissue oxygen consumption are critical. Various techniques have been used to either increase oxygen delivery to the tissues or to decrease the tissue requirements for oxygen. The body's own physiological response, the right shift of the oxygen dissociation curve, does not occur until the haematocrit reaches 8–10%[4]; this correlates to a haemoglobin of approximately 2.8 g dl^{-1}. Some workers have used active cooling to achieve the twin goals of decreased metabolic requirement for oxygen and increased oxygen delivery, as the amount of oxygen dissolved in the plasma increases with decreasing temperature.[5] There is evidence to suggest that active cooling causes a marked leftward shift of the oxygen dissociation curve, thus reducing the amount of oxygen released to the tissues.[6] Another disadvantage to active cooling is that it impairs haemostasis.[7]

Perfluorochemicals have been used to augment oxygen transport in a Jehovah's Witness patient.[8] These substances have a short circulatory half-life and their oxygen tension and partial pressure relationship is linear, thus requiring the use of 100% oxygen. Perflurochemicals have been used to increase the yield of blood taken for autologous transfusion immediately before surgery. The use of hyperbaric oxygen has also been suggested to increase dissolved oxygen in the plasma.[9] Fortunately, in this patient, there was an improvement in the global markers of tissue oxygenation and perfusion.

Although our patient did not suffer large postoperative blood loss, in retrospect, the administration of an anti-fibrinolytic drug such as tranexamic acid or aprotinin and the use of desmopressin to boost factor VIII levels may have been useful to reduce postoperative oozing.[10]

Although a Jehovah's Witness has survived with a haemoglobin as low as 1.6 g dl^{-1} after major trauma, he was significantly younger at 29 yr old than this patient of 67 yr.[11] Other major elective procedures with large anticipated blood loss have been performed in Jehovah's Witness patients though with the benefit of preoperative optimization of haematocrit, cell salvage, and in some cases the use of platelets, factor concentrates and human albumin.[12]

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Discovery of left-sided superior vena cava during central venous catheterization

A. G. HIGGS, S. PARIS AND F. POTTER

Summary

We describe a 3-yr-old patient in whom a central venous catheter (CVC) was inadvertently inserted into a persistent left superior vena cava (PLSVC). This congenital anomaly was diagnosed using transthoracic echocardiography. The aetiology and the implications for the anaesthetist are discussed. (*Br. J. Anaesth.* 1998; **81**: 260–261)

Keywords: Veins, catherization; veins, complications; measurement techniques, transthoracic echocardiography

Detailed anatomical knowledge of the great vessels of the neck and thorax is a pre-requisite for safe anaesthetic and intensive care practice. Whilst all anaesthetists are familiar with the clinical anatomy and radiological appearances in the normal patient, few are familiar with the commonest anomaly of the venous circulation—persistent left superior vena cava (PLSVC).[1 2]

We report a patient who underwent uneventful placement of a CVC via the left external jugular vein which produced an unusual, but previously described,[3] appearance on routine post-procedural chest radiograph. Using transthoracic echocardiography the CVC was seen to lie in a hitherto undiagnosed PLSVC.

Case report

A 3-yr-old boy presented to the emergency department having suffered a non-accidental scalding injury. He suffered full thickness scalds affecting both legs, buttocks and hands. There was no other trauma.

He was admitted to the regional paediatric burns unit where, despite all appropriate measures, on the third day he developed systemic sepsis. The patient was admitted to the paediatric intensive care unit (PICU) where, despite aggressive resuscitation, his condition deteriorated. He required inotropic support of his circulation and his lungs were artificially ventilated with oxygen using high frequency oscillation. He developed a clotting defect consistent with disseminated intravascular coagulation.

On day 5, he needed additional venous access. All the channels of the multi-lumen femoral venous line were already in use. The only available site for venous access was his neck. In view of the coagulopathy and the thrombocytopenia (platelet count 17×10^9 litre^{-1}), central venous access was obtained aseptically via his left external jugular vein. This was accomplished uneventfully, other than for some slight resistance initially impeding full insertion of the CVC, which was presumed to represent the point at which the left internal jugular vein passes medially to join the right internal jugular vein. However, routine post-procedural chest x-ray showed that the CVC followed a left para-mediastinal course from the left neck (fig. 1).

The transduced waveform was compatible with placement of the tip in an intrathoracic vein. Blood-gas samples drawn freely from the CVC and femoral venous catheter were indistinguishable and were different from a contemporaneous femoral arterial sample. Although we had excluded extravascular and arterial placement, we were still unsure as to its precise location. We were reluctant to remove the catheter because of the coagulopathy and alternative sites were scarce. A two dimensional transthoracic echocardiogram demonstrated the CVC line in the PLSVC, with the tip lying at the coronary sinus. The heart and great vessels were otherwise structurally unremarkable and the right SVC was present. The

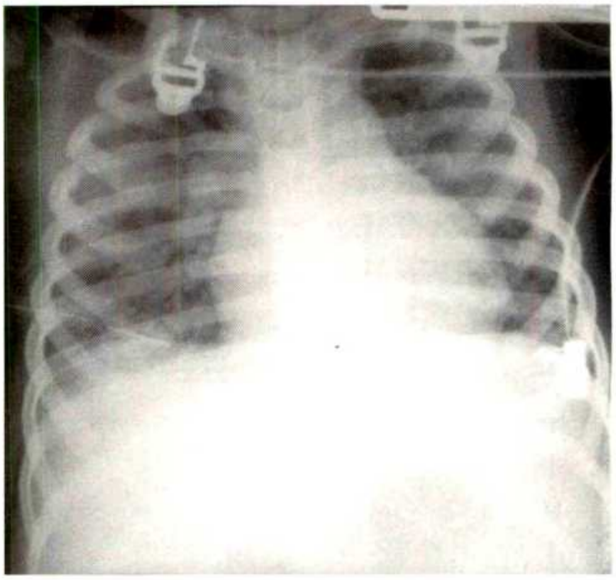

Figure 1 Chest radiograph showing a CVC taking a left para-mediastinal path from the left cervical area suggestive of, but not exclusive to, a PLSVC. Note the diffuse alveolar shadowing consistent with acute respiratory distress syndrome, and the presence of a tracheal and nasogastric tube, ECG leads and a right chest tube draining a right-sided pleural effusion.

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CVC was retracted 2.5 cm in order to avoid complications related to irritation of the coronary sinus.[4]

The catheter was then used uneventfully for TPN administration for the next six days. Removal was not difficult. The child made a full recovery from the episode of septic shock but did require amputation of his non-viable left hand secondary to scald-induced dry gangrene. There was no evidence of impaired venous drainage of the left upper limb.

Discussion

Persistent left superior vena cava is the commonest anomaly of the venous circulation with an incidence of 0.3% in healthy patients and 4.3% in those with congenital heart disease.[1 2 5] It is most frequently associated with ASD, cor triatriatum and mitral atresia. John Marshall gave the first embryological explanation for PLSVC in 1850.[6] The right SVC enters the right atrium on its superior aspect. The left SVC drains into the left portion of the sinus venosum or coronary sinus. The lumen of the left SVC is usually obliterated in late embryonic life because of compression between the left atrium and the hilum of the left lung. Reduction of these compressive forces—as occurs in the three anomalies with which the condition is associated—leads to persistent patency of the vessel.[7]

In excess of 80% of PLSVCs co-exist with a right SVC[5] and as most central catheters are placed on the right this probably explains why the anomaly is so rarely reported. Ninety-two per cent of PLSVCs drain into the coronary sinus and thence into the right atrium.[8] In this circumstance, the coronary sinus is usually large because of the increased blood flow through it. The remainder drain into the left atrium and so create a right-to-left shunt.[9] This variant presents the greatest potential hazard for CVC placement, as a cannula in the PLSVC would then give rise to a danger of systemic embolization of air or thrombus.

There are seldom any clinical signs or symptoms of a PLSVC but Cha and Khoury [10] claim the diagnosis is suggested by features on plain x-ray, such as widening of the aortic shadow, para-median bulging and a para-median strip or crescent along the left heart border. However, these appearances are inconsistent and were not seen in the AP mobile film taken of this patient. Rare cases of PLSVC draining into the left atrium have caused unexplained cyanosis or clubbing.[11]

Various problems have been encountered in patients with PLSVC. Manipulation of a CVC in or through the narrow coronary sinus may be difficult and occasionally fraught: manipulation of the coronary sinus has resulted in hypotension, angina and cardiac arrest.[12] The abnormality can also make difficult an attempt to place a pulmonary artery catheter or pacemaker lead into the pulmonary artery or right ventricle respectively, because of the orientation of the coronary sinus. There may be a higher incidence of arrhythmias in these patients.[13] The radiographic appearances produced by insertion of a CVC into a PLSVC may be mistaken for arterial placement, location outside the central venous circulation or an entirely extravascular site.

Diagnosis of arterial placement is made with pressure waveform and blood-gas analysis and is not difficult. In contrast, exact localization of a proven intravenous catheter requires echocardiography. We used 2-D transthoracic echocardiography (TTE) and readily identified all the relevant anatomy, but other authors[14] have highlighted the superiority of contrast transoesophageal echocardiography in patients with a high transthoracic acoustic appearance and/or in mechanically ventilated patients. Bedside echocardiography is safer and more convenient than line-venogram as it is non-invasive and will not cause further haemodynamic instability in a sick patient. This method also excludes the possibility of dextrocardia.

We threrefore recommend echocardiographic examination of a CVC whose precise location is not obvious on routine chest x-ray. This examination allowed us to continue to safely use a CVC placed in a PLSVC and avoid the potential complications of removing the catheter or of producing damage to the coronary sinus. The possible existence of a PLSVC should be considered in a patient where particular resistance to insertion of a CVC is noted when using the left jugular route.

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Transoesophageal echocardiography in the management of whole lung lavage

C. C. McMahon, T. Irvine and I. D. Conacher

Summary

The effects of two lung ventilation, one lung ventilation and alveolar lavage on right ventricular mechanics in a patient have been observed using transoesophageal echocardiography (TOE). Alveolar lavage resulted in additional stresses to those of one lung ventilation (OLV) and the point when these were noted to be resulting in right ventricular changes was used as the signal to terminate the filling phase of a cycle of alveolar lavage. A significant increase in right ventricle afterload occurred on starting OLV. The response to lung lavage was biphasic, initially a further increase in afterload followed by a reduction in preload. Because there was rapid adaptation to these changes, it was felt appropriate to perform sequential lung lavage during the same anaesthetic. In similar circumstances where pulmonary vascular resistance is changed, information obtained from TOE may be used to guide therapy. (*Br. J. Anaesth.* 1998; **81**: 262–264)

Keywords: measurement techniques, transoesophageal echocardiography; lung, lavage

Patients with increased pulmonary vascular resistance, secondary to chronic lung disease, may develop right heart dysfunction with disease progression or as a result of medical intervention, such as positive pressure ventilation and single lung ventilation. We have observed the right ventricular responses to the early effects of three interventions in a patient with a normal heart.

Case report

A 37-yr-old female with a history of pulmonary alveolar proteinosis (PAP), presented for a third session of whole lung lavage (WLL) because of deteriorating lung function. There was no clinical, electro- or echocardiographic evidence of associated right ventricular dysfunction. After her consent, we attempted to monitor the process and assess the risks of proceeding to a sequential single lung lavage during the same anaesthetic using transoesophageal echocardiography (TOE).

Induction of anaesthesia was with propofol, fentanyl and vecuronium, and a left-sided double lumen tube placed. A left radial artery cannula was inserted. Maintenance of anaesthesia was with propofol infusion[1] and the lungs were ventilated with an $F_{I_{O_2}}$ 1.0 and a minute ventilation of 100 ml kg^{-1} during all stages. With the patient supine, a 5MHz multiplane transoesophageal probe, connected to a Hewlett Packard Sonos 1500 imaging system was passed into her oesophagus. The probe was advanced into the stomach until the standard short axis view of the left ventricle at the level of the papillary muscles was obtained. This was used as the mark for the short axis image of the right ventricle.

Observations were made when the patient was stable during two lung positive pressure ventilation, during left single lung ventilation (SLV), and throughout lavage of the right lung. Automated detection of the endocardial border (ABD) allowed real-time display of the data for right ventricular end systolic area (ESA), end diastolic area (EDA) and fractional area change (FAC), calculated on line as FAC = (EDA–ESA)/EDA. One representative ventilation cycle during each stage of ventilation was identified and the value of each variable was taken for every heart beat during the full ventilation cycle (from peak inspiration). Normality of data was evaluated using the Anderson-Darling test and the means, calculated for each cycle, were compared using the two-tailed Student *t* test (Minitab Inc., Release 11.2)

Results

The means of EDA, ESA, and FAC are tabulated (table 1) and reported as representative values for right ventricular function during baseline two lung ventilation, during change to OLV (transition period—on acute clamping of double lumen tube), and established on OLV before right lung lavage.

Figure 1 summarizes the changes that were observed during the first lavage cycle of 1 litre of saline. Again, the mean of each variable is shown, as calculated for one ventilation cycle from each 15 s as the lavage progressed, and for the first 30 s of drainage after filling the lung with warmed, buffered normal saline.

Systolic arterial pressure decreased from 136 mm Hg on OLV to 78 mm Hg at the end of the first filling phase, with recovery to 124 mm Hg on emptying the right lung. Peripheral oxygen saturation was 99% throughout both phases.

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Table 1 Changes in right ventricular dynamics as left single lung ventilation is established. (**$P<0.01$ compared with two lung values)

Stage	Mean EDA (cm^2)	Mean ESA (cm^2)	Mean FAC
Two lung IPPV	6.5	4.8	26.2%
Range	(5.8–7.0)	(4.0–5.4)	(22%–31%)
Transition period	6.4	5	21.5%
Range	(5.8–6.7)	(4.6–5.3)	(18%–26%)
(% difference from two lung values)	(–1.5)	(4)	(–18)
Single lung IPPV	7.5**	6.1**	18.3%**
Range	(7.4–7.7)	(5.9–6.3)	(15%–21%)
(% difference from two lung values)	(15)	(27)	(–30)

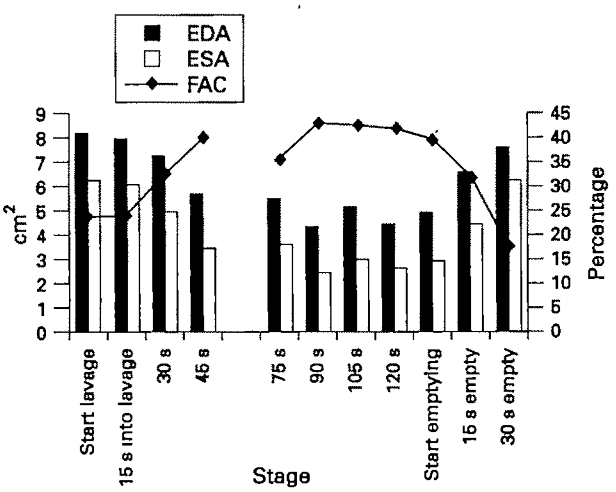

Figure 1 Changes in right ventricular dynamics during the first cycle of the whole lung lavage of the right lung. The lack of data at 60 s is because of physiotherapy at that time.

Discussion

The right ventricle is difficult to study using standard imaging techniques because of its complex structure. Animal studies have shown that right ventricular area assessed with ABD reflects changes in right ventricular volume and that the relationship between cross-sectional area and volume varied little with changes in left ventricular volume.[2] Two dimensional echocardiography may be more sensitive to changes in volume and pressure loading than pulmonary artery flotation catheters.[3] However, in patients whose lungs are ventilated, inflated lung can restrict the available acoustic windows and limits transthoracic echocardiographic examination. TOE is therefore more useful for studying right ventricular responses during positive pressure ventilation.

The most marked change seen on starting single lung ventilation is a 30% reduction in FAC, associated with a progressive dilatation of the right ventricle, initially at end-systole, but then also at end-diastole (table 1). It is not possible to determine the significance of this isolated observation in terms of normality though the predominance of systolic dilatation on transition suggests that the fall in FAC is primarily a reflection of a change in right ventricular afterload imposed by an increase in pulmonary vascular resistance when the total tidal ventilation is applied to one lung. The data confirm that this manoeuvre may represent a significant insult to a normal right ventricle and is of relevance to the effects of acute clamping of double lumen tubes in the conduct of anaesthesia for pulmonary surgery in those whose right ventricles are compromised.

PAP is a very rare condition in which there is accumulation of a PAS-positive substance in the alveoli resulting in deterioration in efficiency of gas exchange, the development of respiratory failure and ultimately cor pulmonale. WLL is the only treatment shown to be of therapeutic benefit.[4] This procedure is conducted under general anaesthesia and involves the filling of one lung with 0.9% saline under pressure (15 cm H_2O) and then allowing it to drain passively to FRC, and repeated until the drained fluid is no longer turbid with proteinaceous material. It is common practice to wash out only one lung at a time, and repeat the procedure on the other lung at some time later. In animals and in humans, this controlled drowning process is associated with an acute and cyclical rise in pulmonary vascular resistance.[5 6]

The echocardiographic experience is that WLL is initially associated with an additional increase in pulmonary vascular resistance, greater than that resulting from single lung ventilation, which caused the right ventricle (fig. 1) to dilate further. Initially, FAC remains unchanged. As lavage volume increases, EDA and ESA decrease (–45% and –58% respectively). This pattern is in keeping with a reduction in right ventricular preload and reflects the effect of intrathoracic pressure on systemic venous return. The increase in FAC (+75%) is suggestive of an increase in right ventricular systolic function but as the FAC is a function of a smaller EDA (by inference, end-diastolic volume), it is not possible to interpret the net effect on right ventricular stroke volume.

Data at 60 s are missing because it is when physiotherapy was used to improve the washout yield of proteinaceous material. An increase in heart rate was seen during the lavage (85 beat min^{-1} during single lung ventilation to 115 during WLL) and it is possible that the tachycardia represents the stimulation of this manoeuvre, but as there was no other evidence of inadequate depth of anaesthesia we consider the commensurate increase in heart rate to be the result of the autonomic response to the lavage.

As the lung emptied, the effect on preload was reversed and the right ventricle dilated, initially to two lung ventilation values, but returning to OLV values as the afterload effect of ventilating one lung is again the predominent influence.

The initial 1 litre volume of washout had produced visible alterations in right ventricular function so it was decided that the observation of reduced heart areas would be the marker for the fluid volume limit for each subsequent lavage cycle. By setting the limits to lavage volume to the level where significant right ventricular changes were apparent (approximately 35–50% reduction in EDA), and by demonstrating the rapid adaptation and recovery of the right ventricle to the various stresses imposed, TOE aided the decision to proceed to lavage of the second lung during the same anaesthetic. The whole therapy with 500- to 750-ml aliquots of saline to a total of 15-litre washout to each lung was undertaken without incident and decreases in systolic arterial pressure were not seen during the filling phases. At follow-up, there was therapeutic benefit, subjectively and in pulmonary function tests (oxygen saturation on air from 90% to 96%: FEV_1/FVC 1.71/2.19 to 2.12/2.67).

In detailing the responses of a normal right ventricle to inflationary loads, TOE proved useful in defining alterations in right ventricular afterload and preload, and assisting clinical judgement in deciding safety limits of therapy. Other clinically imposed stresses affecting the pulmonary vascular bed in which a window on right ventricular mechanics would be of great value to optimize therapy include the use of PEEP in acute lung injury, positive pressure ventilation in cor pulmonale and systemic vasoconstrictors in pulmonary hypertensive disease. TOE of the right ventricle has great potential as a guide to the most appropriate form of ventilation for an individual with cardiopulmonary disease.

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Use of remifentanil in a patient with chronic hepatic failure

L. Dumont, V. Picard, R. A. Marti and E. Tassonyi

Summary

We describe a 73-yr-old woman anaesthetized for a laminectomy. She suffered from hepatic failure with mild encephalopathy complicated by several exacerbations associated with sedative and opioid therapy. The challenge for anaesthesia management was to provide adequate analgesia and avoid causing hepatic encephalopathy during and after the surgery.We used remifentanil to provide intraoperative and postoperative analgesia, because it has a short duration of action and does not require hepatic metabolism. We closely monitored the respiratory and the neurological status throughout the administration and conclude that remifentanil can provide perioperative analgesia in patients at risk of developing hepatic encephalopathy. (*Br. J. Anaesth.* 1998; **81**: 265–267)

Keywords· liver, cirrhosis; anaesthetics volatile, isoflurane, analgesics opioid, remifentanil; anaesthetics i.v., propofol; complications, hepatic encephalopathy; pain, postoperative; surgery, laminectomy

Remifentanil is licensed in Switzerland for use as an analgesic in the immediate postoperative period, with the supervision of staff trained in the recognition and treatment of the respiratory effects of powerful opioids.

Case report

A 73-yr-old woman suffered from a painful arachnoid cyst at the thoracic level, with a Brown–Séquard syndrome. She was being treated with tramadol (Tramal, Grünenthal), morphine (MST Continus, Mundipharma) and ibuprofen (Brufen, Knoll Pharmaceuticals). She had a 10-yr history of hepatitis C complicated by cirrhosis with frequent minor episodes of memory loss, mild confusion and irritability. She had experienced three episodes of severe hepatic encephalopathy in the preceding eight months, associated with administration of sedative or opioid drugs. The first one was precipitated by a minor gastric ulcer haemorrhage and diazepam (Valium, Roche) medication. The two other episodes occurred without gastrointestinal haemorrhage, but in association with morphine or tramadol administration. Each episode resolved satisfactorily with lactulose, a low protein diet and removal of the likely precipitating drugs. The clinical features of these episodes and EEG findings were characteristic of hepatic encephalopathy rather than simple opioid intoxication.

In order to alleviate her continuous pain, and reduce the drug treatment, surgical resection of the cyst was planned.She had portal venous hypertension, oesophageal varices, and hypersplenism. She had abnormal coagulation factors: prothrombin time: 34 s (normal range: 25–32 s) with factor V at 80% and hypoalbuminaemia (30.8 g litre^{-1}); a platelet count of 74 000 per l. Plasma electrolytes and bilirubin were normal. Her general clinical state was good, with no evidence of ascites. Her weight was 75 kg, arterial pressure was 130/70 mm Hg and heart rate 80 beat min^{-1}.

The patient did not receive premedication. Anaesthesia was induced with propofol 2 mg kg^{-1} (Disoprivan, Zeneca), remifentanil 1 μg kg^{-1} (Ultiva, Glaxo Welcome) and intubation was facilitated by atracurium 0.5 mg kg^{-1} (Tracrium, Glaxo Welcome). Anaesthesia was maintained with 50% nitrous oxide/oxygen, isoflurane 0.5–0.8 MAC (Forene, Abbott) and remifentanil infusion at a rate of 0.25 to 0.5 μg kg^{-1} min^{-1}. The monitoring included ECG, arterial pressure by the radial artery catheter, pulse oximetry, rectal temperature, and anaesthetic gas and carbon dioxide analysis. One hour before operation the patient received platelet concentrates and fresh frozen plasma to correct the blood coagulation defect. Intraoperatively 2 litres of crystalloid (glucose 5%-NaCl 0.45 %) were administered. After induction of anaesthesia, a decrease in arterial pressure to 85/40 mm Hg necessitated administration of i.v. ephedrine 10 mg to restore the arterial pressure to the preinduction value. Otherwise haemodynamic parameters, blood–gas analysis, blood glucose and electrolyte plasma concentrations remained in the normal range throughout the operation. The duration of the laminectomy was 90 min and the blood loss was minimal.

The remifentanil infusion, isoflurane and nitrous oxide were stopped after skin closure and the lungs ventilated with 100% oxygen. Spontaneous respiration returned 4 min later and the trachea was extubated after 7 min. Immediately after awakening, the pain intensity verbal rating score (VRS; 0=no pain, 10=maximum pain imaginable) was zero. Seven minutes later, upon the arrival at the recovery room, the VRS was 7 and a continuous infusion of remifentanil was started at 0.15 μg kg^{-1} min^{-1} and the VRS returned to 2 within 7 min. We recorded the VRS

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every 15 minutes during the first 2 h and each hour thereafter. Respiratory rate was monitored throughout the remifentanil infusion. We assessed the neurological status and the presence or absence of flapping tremor every 2 h during the first 48 h and two times a day thereafter. The remifentanil infusion was continued for 48 h in the recovery room at a rate of 0.040 to 0.075 μg kg^{-1} min^{-1} depending on the patient's complaints and the VRS. In view of the absence of neurological impairment, ventilatory depression, and the good quality of analgesia, we continued the remifentanil infusion in the ward for 5 days with pulse oximetry and respiratory rate monitoring. Other treatment consisted of a low protein diet (<40 g a day) and oral lactulose. Surgical progress was normal and the patient was discharged after 8 days.

Discussion

Hepatic encephalopathy is not a typical complication of general anaesthesia,[1] but may be related to the use of opioids after operation in patients with severe liver dysfunction.[2] The challenge in our patient was to ensure adequate intraoperative analgesia and postoperative pain relief, without affecting liver function or causing encephalopathy. Regional anaesthesia with local anaesthetics could have been useful but was contraindicated in our patient who had a coagulation defect.[3] We therefore decided to perform general anaesthesia based on nitrous oxide/oxygen, remifentanil and supplemented by isoflurane and atracurium.

Remifentanil is a mu receptor agonist with analgesic potency similar to fentanyl. It is metabolized by non-specific circulatory and tissue esterases and has a rapid elimination rate.[4 5] Remifentanil has been studied in patients with severely compromised hepatic function. In these patients the metabolism of remifentanil was not altered and hepatic encephalopathy did not occur.[6] We therefore decided to use remifentanil not only during the operation but also for the postoperative analgesia.

The induction of anaesthesia with propofol and remifentanil provoked a 40% fall in arterial pressure which was rapidly corrected. Otherwise haemodynamic stability was preserved during the operation. Perhaps a smaller dose and slower administration of both drugs might have reduced the hypotension observed on induction of anaesthesia.

Non-steroidal anti-inflammatory drugs are contraindicated for pain relief after operation in patients with liver disease.[7] Two recent studies compared remifentanil and morphine for early postoperative analgesia and showed that remifentanil gave adequate analgesia but with a higher rate of ventilatory depression.[8 9] Morphine has been largely studied in patients with liver disease and it appears that despite its unchanged metabolism in these patients, there is an increased end-organ sensitivity to this drug.[10] The choice of remifentanil instead of morphine as a postoperative analgesic was based on its rapid elimination if early signs of encephalopathy appeared, on its complete extrahepatic metabolism and on the absence of induced hepatic encephalopathy reported in a recent study.[6] The postoperative infusion rate varied between 0.040–0.075 μg kg^{-1} min^{-1}, which was the recommended range for healthy patients and slightly higher than for patients with liver disease.[5 6] We monitored the patient for the appearance of asterixis. Flapping tremor is a good and reliable indicator of hepatic encephalopathy.[11] We did not perform psychomotor tests to detect encephalopathy as they are very difficult to use in the postoperative period.[12] Neither flapping tremor or other signs of neurological impairment appeared after operation in this patient, who had previously developed encephalopathy following opioid administration.

Several pharmacological and pathophysiological factors may contribute to the development of hepatic encephalopathy, which include increased plasma ammonia, aromatic amine and mercaptan levels, altered GABA sensibility, and administration of benzodiazepines and opioids.[13 14]

The effects of opioids are not clear, but like other sedative drugs, they may worsen a pre-existing neurological impairment.[12 14] Moreover, opioids decrease the propulsive activity of the intestinal tract, so that faecal material remains in the large intestine for a longer time, causing an increased production and resorption of ammonia.[15] Increased ammonia can cause encephalopathy in patients with cirrhosis.[13 14] There is little information concerning the effect of remifentanil on the gastrointestinal tract but it is probable that this mu agonist has a morphine-like effect. Remifentanil was administered continuously during six days and under these conditions the risk of encephalopathy could not be excluded. However, despite its prolonged administration, we did not observe any neurological symptoms characteristic of hepatic encephalopathy.

Remifentanil is 70% protein bound, probably by alpha-1-acid glycoprotein. We may reasonably assume in this patient with liver disease and reduced plasma proteins, that alpha-1-acid glycoprotein was reduced. Thus the possibility of an overdose caused by an increased free fraction of remifentanil was considered and we carefully titrated the drug to prevent respiratory and neurological complications. Most of the time the administered dose was kept in the range of the usual recommended dose, both during and after the operation.[4 5 8 9]

The other drugs used during anaesthesia are known to have minimal effects on liver function. Isoflurane is known to preserve the total hepatic blood flow and hepatic oxygen supply better than other inhalation anaesthetics at one MAC. Its metabolization is small, minimizing the risk of severe hepatic injury.[17]

A single induction dose of propofol did not prolong the recovery time in cirrhosis.[18]

Atracurium is not dependent on liver function for its elimination. However, the main metabolite, laudanosine, may accumulate in the presence of hepatic impairment and can produce central nervous system excitation.[19] This has never been described to our knowledge following atracurium for intubation.

This case illustrates the successful and safe use of remifentanil for analgesia in a patient with chronic hepatic impairment at high risk of acute hepatic encephalopathy. However, this drug is a powerful analgesic agent which should be used cautiously with adequate respiratory monitoring in a high dependency ward, especially in patients with hepatic impairment who may have a greater sensitivity to the side effects of the drug.

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COMMENTARY

Evaluation of flexible (part-time) training in anaesthesia

P. M. SCRIVEN

Summary

One hundred and six former or current flexible trainees in anaesthesia responded to a questionnaire evaluating their part-time training (a response rate of 71%). They were compared with a group of 32 flexible trainees in obstetrics and gynaecology. Anaesthetists were more satisfied than obstetricians and gynaecologists with their training (96% compared with 84%); opportunities to publish (75% and 63%); research training (63% and 48%); and monitoring of their progress (78% and 67%). Without flexible training, 20% of the anaesthetists would have ceased to train, compared with 9% of the obstetrics and gynaecology group. Nearly all those who had finished their training were working as consultants (54% of the whole group); 4% had either retired, become a clinical assistant or a locum consultant. The remainder (42%) were senior registrars. (*Br. J. Anaesth.* 1998; **81**: 268–270)

Keywords: training, flexible; training, evaluation; anaesthesia, general

It is important to retain as many doctors as possible within medicine. Each doctor is expensive to train (approximately £180,000 over 5 yr). If a doctor is unable to continue in medical practice, there is a waste of investment, and also of the skills and potential of the doctor involved. For women pursuing careers in medicine, the biggest problem is the conflict between family and career.[1–3] Long, demanding hours at work may lead to postgraduate trainees giving up a medical career. Flexible (part-time) training may retain some of these doctors, as most flexible trainees are women with small children. Other reasons for both men and women choosing flexible training include disability, ill-health, or caring for a dependent relative.

Criticisms of flexible training include doubts about the quality of training, and therefore of the quality of the doctors produced.[4] Part-time senior registrars in obstetrics and gynaecology evaluated the quality of their training and 81% of the doctors concerned thought their training was as good, or better, than full-time training.[5] In the South West region of England, 18 of the 26 senior registrars who had trained flexibly were appointed to consultant posts.[6] Flexible training must have produced doctors capable of being appointed to the consultant grade.

As medical schools in the United Kingdom are admitting more women than men, the number of flexible trainees can be expected to increase. This study was designed to evaluate higher professional training in anaesthesia from the perspective of the flexible trainee, and compare this with the findings of Fiander's group in obstetrics and gynaecology.[5]

Methods and results

Fiander's questionnaire was modified so that it was appropriate for anaesthesia. It includes sections on personal details, reasons for choosing flexible training and attitudes related to part-time training. Respondents were asked to comment on deficiencies and difficulties encountered and the quality of training received. Outcome was assessed by asking about current post or career aspirations. Open and closed sections were used and opportunities provided for respondents to supply further details. The potentially misunderstood statement "I do not regret training part-time" was replaced by "I regret training part-time".

Quantitative data were analysed by frequency analysis and qualitative data by categorizing the content analysis, categorization and summary. Twenty attitudinal statements were analysed by frequency analysis.

To preserve confidentiality, the Royal College of Anaesthetists agreed to distribute the questionnaire to all current and previous flexible higher specialist trainees. Of 151 questionnaires, 106 were returned complete: a 71% response rate. In addition, one questionnaire was returned unanswered as the doctor had retired and felt the information would be irrelevant. Demand for flexible training has increased, with 43 (40%) of the anaesthetists questioned starting flexible training from 1991 to 1996, and the remaining starting from 1969 to 1990.

GROUP CHARACTERISTICS

Nearly all of the doctors were married, 99 of 106 (93%), and just over half, 56 (54%) were married to other doctors. The size of the family depended on parental age, so many of those who had started flexible training recently were younger and had one very young child. Overall, 62 (59%) had two children, and only two had more than four children.

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Table 1 Attitudes to part-time training (In order of agreement/disagreement)

	Agree	Tend to agree	Unsure	Tend to disagree	Disagree
Part-timers generally work more than their specified hours.	74	25	4	3	–
The quality of part-time training is as good as full-time training.	57	36	8	5	–
An opportunity for research should be an important component of part-time training.	66	24	6	7	2
Part-timers are as likely as full-timers to develop sub-specialty interests.	69	20	5	9	3
Part-timers are as likely as full-timers to feel the effects of stress at work.	69	18	4	10	5
Full or part-time, the end product is the same.	59	25	12	8	2
There is prejudice against part-time training.	42	41	4	16	3
Limited geographical mobility is a problem for part-timers following accreditation.	49	33	8	10	6
Part-time trainees are viewed as less committed than full-time trainees.	35	40	6	14	11
Part-timers have to compete with full-timers for clinical experience	46	28	2	19	10
Setting up part-time training is unnecessarily complex.	39	23	5	28	10
Part-time training takes too long.	40	23	7	24	12
Part-time trainees receive poor financial remuneration.	38	25	9	19	15
It is easy to become frustrated with part-time training.	32	35	5	26	8
Ultimately, a part-timer is as likely as a full-timer to get the job they want.	32	23	25	18	8
I have experienced discrimination as a part-time trainee.	28	21	8	19	30
Continuity of care is a big problem with part-time training.	13	12	7	41	32
I regret training part-time	5	3	4	16	78
Anaesthetic competence suffers as a result of being part-time.	1	5	4	22	74
Part-time training is an easy option	–	1	1	26	78

BACKGROUND TO PART-TIME TRAINING

More of the doctors, 66 (63%), had taken a career break, usually because of having children. Family commitments were given as the reason why 101 (96%) had wanted to train flexibly. Other reasons were partner's career; improved hours; disability and ill-health; and geographical restrictions.

Fifty-two (49%) had encountered delays before starting part-time senior registrar posts. These were mainly because of maternity leave, funding or educational approval. This was a particular problem in Scotland where one doctor had had to wait three years.

PART-TIME POSTS

The majority, 80 (74%), worked between five and seven sessions per week, with 20 (19%) working eight sessions. Only three worked less than five sessions, and three worked nine sessions. Up to 16 additional duty hours per week were worked by 71 (67%) of flexible trainees. At the time of the survey 57 (54%) were working either full-time or part-time as consultants; and 45 (42%) were working as senior registrars, with 4% either retired or working as a clinical assistant or locum assistant.

QUALITY OF TRAINING

One hundred flexible trainees (96%) were satisfied with their training and of these, 39 (37%) were very satisfied. Ninety trainees (86%) in anaesthesia usually had protected teaching sessions (that is, not changed to cover service requirements); 83 (80%) considered they had adequate training in teaching; and 51 (48%) adequate management training responsibilities. Seventy-eight trainees (75%) had opportunities to publish research, and 66 (63%) reported that they had adequate research training. Progress was thought to be monitored adequately by 81 trainees (78%). Despite the generally positive reports on flexible training, 61 (58%) considered there were deficiencies in it.

IMPROVEMENTS TO PART-TIME TRAINING

Some respondents commented that the general quality of training had improved since they had been flexible trainees. Some trainees in anaesthesia wanted more supervision and guidance. A few trainees wanted better recognition of the hours worked, and recovery time after a night on-call.

ATTITUDES TO PART-TIME TRAINING

The responses to attitudinal statements, arranged in order of agreement/disagreement are shown in table 1. In addition, these statements were grouped into those dealing with issues of quality, prejudice or problems related to part-time training, and the scales were collapsed into agreement, unsure, and disagreement.

Quality of training: Ninety-three trainees (88%) thought that the quality of part-time training was as good as full-time training. The development of sub-specialty interests was thought to be as likely for part-timers as full-timers by 89 (84%) of those questioned. Eighty-four trainees (79%) considered that the end-product of part-time training was the same as that of full-time training. By contrast, the likelihood of a part-timer getting the job they wanted was less certain; 55 (52%) thought that they would. Ninety-four anaesthetists (89%) disagreed with the statement "I regret training part-time".

Prejudice: 83 flexible trainees (79%) thought this was present. Discrimination was experienced by 48 (45%).

Problems: 104 (98%) of anaesthetists disagreed with the statement that part-time training is an easy option. Similarly, 96 (91%) disagreed with the statement that clinical competence suffered as a result of part-time training. Seventy-three (69%) disagreed that continuity of care was a big problem. A further 63 (59%) thought part-time training takes too long.

From analysing free text comments, prejudice and negative attitudes were reported as problematic for 22 (21%) and time conflicts/exhaustion for a further 20 (19%). Scheme administration, problems with arranging domestic support, and low pay were other difficulties. Stress was mentioned by 17 anaesthetists (15%). Geographical difficulties, such as transferring regions, were also mentioned.

ALTERNATIVES TO PART-TIME TRAINING

Twenty-one trainees (20%) would have given up medicine if they had been unable to train part-time; 40 (38%) would have stayed at a lower grade or worked as locums; and only six (5%) would have changed specialty. Forty (38%) would have worked full-time although two respondents predicted personal disasters would have happened as a result of that decision. Fifty-seven (54%) were working or intended to work full-time later in their careers. For those doctors who continue to work part-time, seven sessions (28 standard hours) was the preferred option for 44 (42%).

RECOMMENDING FLEXIBLE (PART-TIME) TRAINING

Part-time training would be recommended to a colleague by 101 anaesthetists (96%), and the remaining five would do so with reservations. The perceived disadvantages were reduced remuneration (and pension rights), discrimination and lack of status, and the prolonged training time.

Discussion

Part-time training has been available in anaesthesia for many years, and so the group studied was considerably larger than that in obstetrics and gynaecology. The poorer response rate from anaesthetists compared with obstetricians and gynaecologists may have been because of the single mailing, and the inability to follow-up non-respondents.

The number of doctors choosing flexible training has increased over the years, and the situation in anaesthesia follows this trend. The group characteristics and background to part-time training for anaesthetists were very similar to those in obstetrics and gynaecology.

On-call commitments for anaesthetists training flexibly were less onerous than that for obstetrics and gynaecology trainees, of whom 50% were on-call for more than 16 ADHs per week. There were many similarities between the two groups. The main difference was that the anaesthetists reported a consistently higher satisfaction with the quality of training: 100 (96%) compared with 24 (86%) obstetricians and gynaecologists. Continuity of care in anaesthesia was not perceived to be a difficulty whereas it was in obstetrics and gynaecology.

Flexible trainees were well motivated and satisfied with the content of their training, with the possible exception of management. Opportunities to publish research were good and trainees were encouraged to undertake it. Supervision was monitored adequately. Flexible trainees choose part-time in preference to full-time training. Thus surveys of flexible trainees usually report good satisfaction ratings.[5,6] Despite the generally positive attitude to quality, deficiencies in training were noted by over half of the doctors in anaesthesia and obstetrics and gynaecology. However, prejudice towards flexible trainees appears to persist with significant numbers in both groups of trainees reporting possible discrimination.

Flexible training in anaesthesia is effective at retaining doctors: otherwise 20% of trainees would have given up, and 38% would have remained at a lower grade, thus wasting the skills and potential of over 50% of the respondents. Nearly all the anaesthetists leaving flexible training achieved career grade posts as consultants suggesting that they were of satisfactory quality.

Appendix

ADDITIONAL INFORMATION

HM(69)6	Established supernumerary posts at any level for part-time doctors. *Ad hoc* arrangements. Regions varieties in uptake.
PM(79)3	Official part-time training for doctors. Senior Registrars only. National scheme.
EL(94)86	Flexible training.
1996	"A Guide to Specialist Registrar Training" ("Orange Guide"). ch. 6. Flexible training.

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CITATION CLASSIC

Commentary

Allison SP, Tomlin PJ, Chamberlain MJ. Some effects of anaesthesia and surgery on carbohydrate and fat metabolism. *British Journal of Anaesthesia* 1969; **41**: 588–593.

This study was carried out at a time when the jigsaw of the neuro-endocrine and metabolic response to injury was incomplete. Its results, when combined with the work of others, helped to complete the picture. The study was stimulated by the observation of intolerance to glucose in the pump priming during cardiopulmonary by-pass surgery.[1] Glucose levels remained high during the operation but fell in the immediate postoperative period, causing a fall in serum potassium concentration as glucose was taken up by cells. The consequent hypokalaemia precipitated arrhythmias in patients who had previously received digoxin. These metabolic changes were found to be caused by impairment of insulin secretion during surgery, with a rise in insulin levels as the immediate stress of surgery was withdrawn. This phenomenon was explained by the work of Porte and colleagues[2] who demonstrated α-adrenergic suppression of insulin secretion during catecholamine infusion. In the cited study, we extended our observations to patients undergoing general surgery and showed that changes in insulin secretion were a non-specific effect of surgical stress rather than a pharmacological consequence of open-heart surgery or anaesthesia. In view of the relationship between the severity of the surgery and the extent of the endocrine and metabolic responses, we concluded that suppression of insulin secretion was mediated by sympathetic nervous activity, although we were unable to block the phenomenon with phentolamine, perhaps because of an understandable diffidence in the dose used.

We subsequently extended these observations to patients with acute illness and trauma.[3] We showed the same suppression of insulin secretion, glucose intolerance and high free fatty acids in the acute phase of injury, followed by a period of persistent glucose intolerance associated with high insulin levels, demonstrating insulin resistance. We concluded that these effects of injury on insulin secretion were features respectively of the ebb and flow phase of the metabolic response to injury described by Cuthbertson.[4] The work of others[5] who described high cortisol, glucagon and catecholamine levels after injury, completed the picture of the endocrine response and went some way to explaining the metabolic consequences of injury.

The full picture of the neuro-endocrine response to injury was completed by studies demonstrating the role of afferent signals from injured tissue, passing via the peripheral nervous system and spinal cord to the hypothalamus which, in turn, acts upon the pituitary and the autonomic centre.[5] Subsequently, the cytokine story unfolded showing that the hypothalamus is also stimulated by circulating factors produced as a result of inflammation. Thus, the complex inter-related pattern of the neuro-endocrine and cytokine response to injury was built up and was able to explain not only Cuthbertson's classic observations of an increase in metabolic rate and a negative nitrogen balance after injury, but glucose intolerance, accelerated hepatic gluconeogenesis and mobilization of fat and protein reserves to meet the demands of repair and recovery.

All these results created a therapeutic dilemma. Is the metabolic response to injury a useful adaptation to promote recovery, or a pathological change to be prevented or suppressed? John Hunter in 1794,[6] in his treatise on blood, inflammation and gunshot wounds, intuitively understood this dilemma when he wrote: "Impressions are capable of producing or increasing natural actions and are then called stimuli: but they are likewise capable of producing too much action, as well as depraved, unnatural or what we commonly call diseased actions." In other words, a response necessary for the survival of the majority, may, when carried to extremes, threaten survival of a few severely ill patients. These considerations have led to two types of intervention strategy; first, attempts in critically ill patients to block or overcome the response to injury by pharmacological, nutritional or hormonal means; second, the use of strategies to minimize the severity of the stimulus or stress and therefore lessen its hormonal, inflammatory and metabolic consequences, hoping to improve outcome and accelerate convalescence. The second has proved the most fruitful approach. Using the hormonal and metabolic changes described above as a measure of the severity of stress, Kehlet and colleagues[7] showed that spinal anaesthesia, by blocking afferent stimuli from the site of the wound, could ameliorate the acute and subsequent changes in patients undergoing surgery in the lower half of the body. Other improvements in perioperative and post-traumatic care have also served to reduce the stimulus.

Our observations explain the so-called "diabetes of injury" and the intolerance of glucose by injured or sick non-diabetic patients. Such patients may have limited tolerance of glucose-containing parenteral or enteral feeding regimens, necessitating reduction in the rate of infusion or even the administration of insulin. They also provide the basis for understanding the effect of illness and surgery on diabetic patients, who require increased doses of insulin to maintain glucose control.

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British Journal of Anaesthesia 1998; **81**: 273–277

Brit. J. Anaesth. (1969), **41**, 588

SOME EFFECTS OF ANAESTHESIA AND SURGERY ON CARBOHYDRATE AND FAT METABOLISM

BY

S. P. ALLISON, P. J. TOMLIN AND M. J. CHAMBERLAIN

SUMMARY

The effects of emotional stress, nitrous oxide and halothane anaesthesia, a 1-minute period of hypoxia, and surgery, on the blood sugar, plasma free fatty acids (FFA) and insulin were investigated. The emotional stress of being brought to the operating theatre and the stress of surgery seem to be more important than anaesthesia in causing a rise in blood sugar and plasma FFA. There was a corresponding fall in levels of plasma insulin. The infusion of phentolamine in two patients did not prevent the failure of insulin response to injected glucose during surgery. The clinical significance of this temporary state of glucose intolerance is discussed.

In a preliminary communication (Allison, Prowse and Chamberlain, 1967), a failure of insulin response to injected glucose during surgery and in the acute phase of myocardial infarction was reported. More recently (Allison, Hinton and Chamberlain, 1968) a similar phenomenon has been demonstrated in burned patients. It was suggested that this effect was a non-specific response to stress, mediated by increased adrenaline secretion and sympathetic activity, in view of the observation by Porte and associates (1966) that insulin response to injected glucose could be suppressed by adrenaline infusion. Porte and associates showed also that suppression by adrenaline of the insulin response to glucose could be prevented by alpha but not by beta adrenergic blockade. The present study was designed to examine the effects of the emotional stress of impending operation, nitrous oxide anaesthesia, hypoxia and surgery on the levels of blood sugar, plasma free fatty acids and immunoreactive insulin (i.r.i.). We also wished to examine further, the failure of insulin response to glucose during surgery and to test the effect upon this of infusing phentolamine, an alpha adrenergic blocker.

PATIENTS

Thirteen patients (age range 23–67 years) undergoing a variety of surgical procedures, ranging in severity from exploration of the common bile duct to stripping of varicose veins, were studied. The patients were divided into three groups.

Group 1.

In 7 patients, a standard 25-g intravenous glucose tolerance test (GTT) (Samols and Marks, 1965) was performed twice; the first test was on the day before the operation, at the same time of day as the operation was expected to take place with the patient under the same fasting conditions. On the day of operation, blood samples were taken in theatre before induction of anaesthesia and 20 minutes after induction, the operation having started. A second i.v. GTT was then performed. No premedication was given in 5 of these patients. Papaveretum and hyoscine was given in one case and pethidine and atropine in another. Anaesthesia was induced with thiopentone (250–350 mg) or methohexitone (70–90 mg) and maintained with nitrous oxide, oxygen and tubocurarine. In 5 patients 2 per cent halothane was used during part of the operation.

Group 2.

In 2 patients the same protocol was adopted as in group 1, except that during the operation phentolamine was infused in 0.9 per cent saline at a rate of 120–150 mg per hour to maintain a systolic arterial pressure of 80–95 mm Hg.

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Group 3.

Blood sugar, plasma insulin and FFA were studied in 4 patients without injection of glucose. Blood samples were taken in the ward, 20 and 10 minutes before the patient was brought to the operating theatre. Further samples were taken 5 and 10 minutes after reaching the theatre and then 10 and 20 minutes after induction of anaesthesia and before the operation had started. The patients were then subjected to 1 minute breathing 5 per cent oxygen, which was sufficient in each case to lower the arterial Po_2 to between 40 and 50 mm Hg as measured with a Po_2 electrode. Samples were taken 1 and 10 minutes following the end of this period of relative hypoxaemia. Finally, blood samples were taken 10 and 20 minutes after beginning the operation. Anaesthetic technique was the same as in group 1 except that in none of the patients was premedication or halothane used.

METHODS

Glucose tolerance tests.

All blood samples were withdrawn from an antecubital vein. A sample was taken for basal levels of blood sugar, plasma FFA and insulin. Glucose 25 g in 50 g/100 ml solution was then injected over 3 minutes into a forearm vein. Blood samples were taken at 2, 5, 10, 20, 30, 40, 50 and 60 minutes after the end of the injection. Pre-operative and operative glucose tolerance tests were compared as follows: (a) in terms of the K value or slope of the logarithmic plot of the glucose curve from 20 to 60 minutes (Samols and Marks, 1965); (b) for insulin response to the injected glucose; and (c) for changes in levels of plasma FFAs.

Blood sugar.

This was measured in duplicate as total reducing substances by the Neocuprin autoanalyzer technique. This is a colorimetric technique involving reduction of a copper salt. Samples were taken into fluoride tubes and estimated on the same day or stored at 4°C until the following day. The reproducibility of this analytical technique is within 2 per cent.

Plasma insulin.

This was measured in triplicate by a modification of the method of Hales and Randle (1963). Samples were taken into sodium heparin tubes and placed in the refrigerator at 4°C pending plasma separation. The plasma was then separated within 2 hours and stored at −20°C until it could be assayed. Samples from both glucose tolerance tests from the same patients were estimated in the same assay. The accuracy of the technique may be gauged by the fact that assays of insulin levels from specimens of pooled plasma measured over a period of 3 months gave a coefficient of variation of 8.5 per cent.

Plasma-free fatty acids.

Blood samples were treated in the same way as for insulin. Plasma was stored at −20°C for a maximum of 24 hours and free fatty acids were then extracted by the method of Dole and Meinertz (1960) and estimated colorimetrically in duplicate by the method of Duncombe (1963). The reproducibility of paired samples was within 5 per cent.

RESULTS

Group 1.

Basal values. The blood sugar rose from a mean level of 86.3 mg/100 ml to a mean level of 94.3 mg/100 ml 20 minutes after induction. The difference is significant ($P<0.01$). The operation had started by the time the second sample was taken, so that it was not possible to distinguish between the effect of anaesthesia and surgery on the blood sugar. It was observed that the level of blood sugar in theatre even before anaesthesia was higher than that found on the ward the previous day in the same patient.

Glucose tolerance tests. Mean values and ranges of blood sugar, plasma insulin and FFA are shown in figures 1A (pre-operative) and 1B (operative), K values being normal, i.e. >1.0 (Samols and Marks, 1965), in all pre-operative tests. In every case the K value was lower for the test performed during operation. In all patients the insulin response to glucose was lower during surgery than pre-operatively. The degree of suppression of insulin response was greater in more severe operations involving laparotomy than in a simple herniorrhaphy or varicose veins operation. For example, a patient of 49 years undergoing exploration of the common bile duct had a pre-operative K value of 2.04 which fell during operation to less

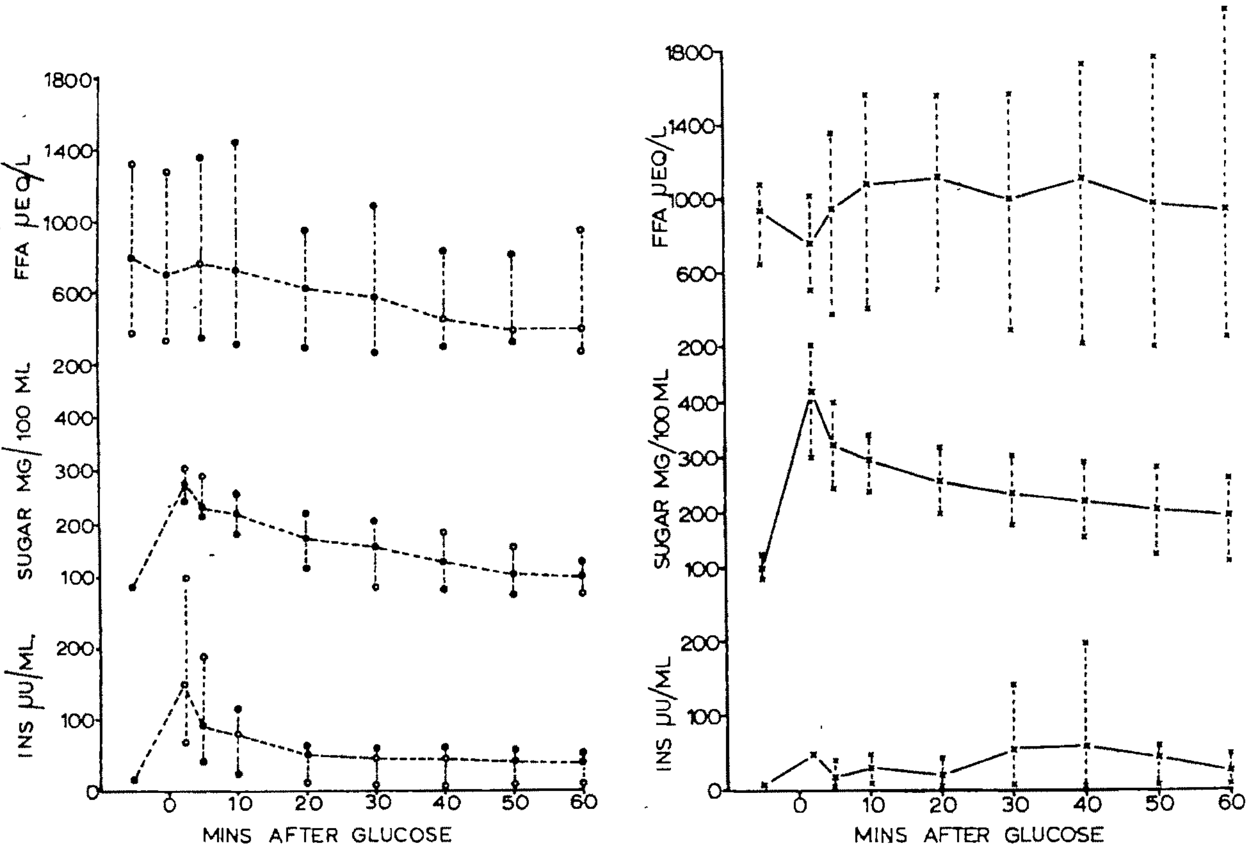

FIG. 1A

Glucose tolerance tests before operation.

FIG. 1B

Glucose tolerance tests during operation.

Mean values and ranges of plasma insulin, blood sugar and plasma FFA are shown before and at intervals after injection of 25 g of glucose (see text).

than 0.1, whereas a similar patient having a stripping of varicose veins had a pre-operative control K value of 3.9 which fell only to 2.0 during operation. The first patient had no insulin response at all during operation whereas the second one had some insulin response to the added glucose, albeit less than in the control study. The later rise in insulin levels seen in figure 1B is due to the fact that in some patients the operation was being completed before the end of the test. The end of the operation is a time when we have previously noticed a rise in insulin levels (Allison, Prowse and Chamberlain, 1967). Plasma FFA levels were higher and the fall in FFA levels less after injection of glucose during surgery as compared with the pre-operative study.

Group 2.

Phentolamine in the 2 patients studied had no apparent effect in preventing suppression of insulin response to glucose. The results from one of the two patients in this group are shown in figure 2. Qualitatively they are indistinguishable from those found in group 1.

Group 3.

The results are shown in table I. Although there is a small rise in blood sugar and FFA following anaesthesia and following the 1-minute period of hypoxia, this is not statistically significant ($P>0.05$). There is, however, a significant rise ($P<0.05$) in both these values associated with moving the patient from the ward to the anaesthetic room and with surgery. The fall in plasma insulin is significant overall ($P<0.01$) but not between each step. There was no statistically significant difference between the members of each pair of values for sugar or FFA within each step and because the time interval between each step was so small (mean 10 minutes); this suggests that the changes in levels of these metabolites were stepwise rather than continuous throughout the period of study.

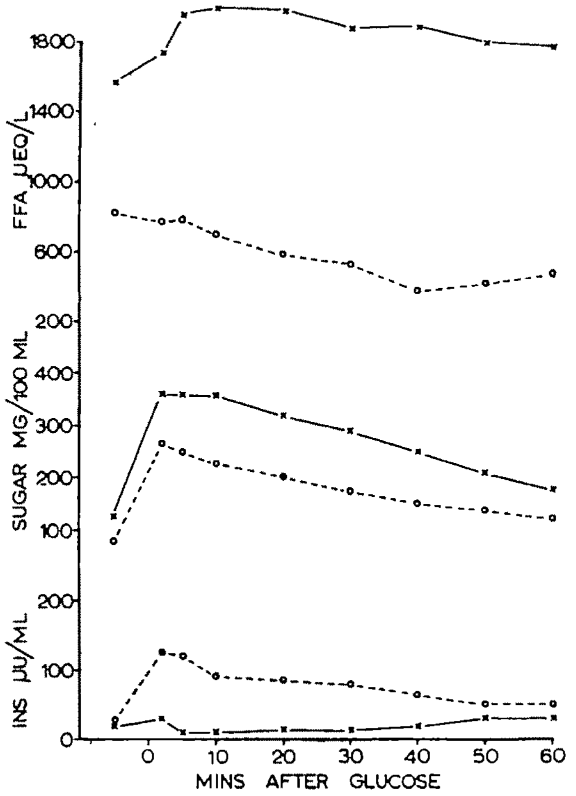

FIG. 2

Glucose tolerance tests before (O......O) and during (X——X) operation. Phentolamine 130 mg/hr infused during operation.

DISCUSSION

There are reports of a rise in blood sugar associated with most anaesthetics. In 1853 Reynoso reported glycosuria associated with ether anaesthesia. Drucker and colleagues (1959) demonstrated glucose but not fructose intolerance under ether anaesthesia. In a recent review, Greene (1968) discussed the effect of halothane and pointed out how anaesthetic management may affect the rise in blood sugar; for example, thiopentone may diminish the hyperglycaemic effects of inhalation anaesthetics. For this reason, it is difficult to assess the effect of nitrous oxide on blood sugar, for it is seldom used alone. With the form of anaesthetic management used in this study, it is clear that the emotional stress of being moved to the operating theatre and the stress of operation were more important factors than was anaesthesia in raising the blood levels of sugar and FFA. The level and length of the hypoxaemia used here was without significant effect on the blood levels of these metabolites, suggesting that the very short episodes of hypoxia sometimes experienced during anaesthesia play no part in the changes described here. Greene (1968) casts doubt on the role of the sympathetic nervous system in the hyperglycaemia associated with inhalation anaesthetics, particularly halothane, and has pointed out that halothane depresses sympathetic nervous activity. Whatever the truth of this argument, it is apparent from the present study that

TABLE I

Mean values (±1 SD) in 4 subjects to show changes in sugar, FFA and insulin levels in the blood.

For explanation of column 2 (Time (min)) see text under Patients (Group 3).

Steps	Time (min)	Sugar (mg/100)	FFA (µ equiv/l.)	Insulin (mµ/ml)
On ward before theatre	20 10	84.8±8.1 84.3±6.7	667±246 656±278	18.3±4.6 18.0±5.7
After taking to theatre	5 10	90.0±4.4 89.5±5.3	855±216 948±237	19.5±6.7 16.0±4.5
After induction of anaesthetic	10 20	92.0±4.9 94.3±9.8	962±279 1074±217	14.3±2.6 14.0±3.7
After 1 minute hypoxia	1 10	98.8±13.6 97.0±12.9	1109±264 1066±205	13.0±2.9 11.5±3.0
After operation begun	10 20	107.5±23.2 114.8±18.2	1231±214 1448±298	11.3±5.3 11.8±6.2

neither thiopentone, nitrous oxide nor halothane was able to prevent the rise in blood sugar and FFA associated with surgery. Neither did they, or the drugs used for premedication, prevent the glucose intolerance and suppression of insulin response to glucose, associated with operation. The changes in blood sugar and FFA could be explained on the basis of increased sympathetic activity causing increased lypolysis and glycogenolysis, but it is apparent that the concomitant suppression of insulin secretion must also affect these values. Porte and associates (1966) demonstrated that the suppression of insulin response to glucose caused by adrenaline could be prevented by phentolamine. In this study the suppression of insulin response induced by surgery was not prevented by phentolamine. It is possible, therefore, that we are dealing with a different mechanism from that described by Porte and associates, but Havel (1968) has pointed out that it is much more difficult to block the effects of endogenously produced catecholamines than those of artificially infused ones. It is possible, therefore, that in this study phentolamine was an insufficiently powerful blocker to prevent insulin suppression. It seemed unjustifiable to use the more powerful drug, phenoxybenzamine, acutely in these patients, in view of its prolonged action and the dangers associated with it. The mechanism of insulin suppression in these patients still remains a matter for speculation, although the rise in insulin level seen at the end of operation in this study and in a previous study (Allison, Prowse and Chamberlain, 1967) seems to suggest that adrenaline mechanism is likely.

The clinical significance of this phenomenon rests on the fact that stress causes a temporary diabetic state. Behaviour in response to infused glucose is different from normal in this situation, causing hyperglycaemia and, by its osmotic effects, expansion of the extra-cellular space and osmotic diuresis. Suppression of insulin secretion also explains partly why mild or latent diabetics show a worsening of the diabetic state as a result of stress. Increased secretion of insulin antagonists, such as growth hormone and cortisol, must also play some part. As described previously (Allison, Prowse and Chamberlain, 1967), in patients on cardiopulmonary bypass in whom large amounts of glucose may be used in the pump priming, the rise in insulin secretion which occurs at the end of operation causes a fall in serum potassium and an increased tendency to digitalis induced arrhythmias.

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ABSTRACTS

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(The name of the author presenting the paper is shown in bold type. *Indicates non-member.)

All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

Assessment of upper airway reactivity following TIVA or inhalation anaesthesia

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The rapid return of upper airway reflexes (UAR) after general anaesthesia is important in order to protect the lower airway from aspiration. It has been shown that UAR may be quantified by determining the threshold concentration of dilute ammonia vapour (NH_3TR) required to cause reflex glottic closure.[1] The aim of this study was to compare the return of UAR after halothane anaesthesia to that following a propofol total intravenous anaesthesia (TIVA) technique.

Twenty healthy males (ASA 1-2, age 17–60) scheduled for elective day case arthroscopic knee surgery were recruited. All were non-smokers, with no history of asthma or recent upper respiratory tract infection. Each subject was allocated randomly to receive either TIVA with propofol or halothane anaesthesia. Anaesthesia was supplemented with 70% N_2O in oxygen. Analgesia was provided using diclofenac 100 mg PR and 0.5% bupivacaine local anaesthesia. At each point of assessment of UAR, an assessment of any residual sedation was also made using auditory reaction time (ART). The ART device measured the time (ms) between an audible buzz through headphones and the patient pushing a small hand held button. The mean of five readings was taken at each point of observation.

Baseline measurements of NH_3TR and ART were taken. Following anaesthesia (time of spontaneous eye opening taken as t=0), further measurements of NH_3TR and ART were taken hourly for 4 h (table 1).

Both groups showed a significant change in NH_3TR and ART following anaesthesia. Subsequent analysis showed a significant increase from baseline NH_3TR and ART at 1 h in the TIVA group. In the halothane group NH_3TR and ART were increased at both 1 and 2 h.

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Table 1 Comparison of TIVA and halothane. Median values (25th–75th centiles). Data were analysed by the Friedmans analysis of variance test for paired non-parametric data followed by Wilcoxon (*P<0.05 from baseline)

		Baseline	1 h	2 h	3 h	4 h
Group 1	ART (ms)	163 (150–190)	196* (170–219)	166 (149–194)	165 (151–194)	159 (147–186)
TIVA	NH_3TR (ppm)	524 (456–908)	939* (524–1447)	701 (308–1097)	524 (308–1035)	524 (308–908)
Group 2	ART (ms)	149 (143–165)	181* (170–228)	165* (150–187)	144 (139–171)	143 (134–171)
Halothane	NH_3TR (ppm)	739 (475–878)	1000* (789–1390)	939* (581–1035)	739 (475–908)	739 (475–908)

A comparison of the effects of sevoflurane and isoflurane on arterial oxygenation during one lung ventilation

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In vitro, sevoflurane inhibits hypoxic pulmonary vasoconstriction in a dose related manner, similar to isoflurane.[1] The purpose of this prospective, crossover study was to compare the effects of sevoflurane and isoflurane on oxygenation (Pa_{O_2}, Sv_{O_2}, and derived shunt) and several cardiovascular variables (HR, MAP, SVR, MPAP, and CO) during one lung anaesthesia.

Sixteen patients scheduled for oesophagogastrectomy were alternately assigned to one of two groups. Patients in group I (n=8) received 1 MAC (1.1%) isoflurane in oxygen from induction until the end of 30 minutes of open chest, one lung ventilation (OLV) in the lateral position. This was followed by 1 MAC (2.1%) sevoflurane in oxygen for the next 30 min of OLV. Patients in group II (n=8) received the inhalational agents in the reverse order. Before induction, an arterial line and a mid-thoracic extradural catheter were inserted. Anaesthesia was induced with propofol 2–3 mg kg^{-1} and fentanyl 1.5 μg kg^{-1}. Neuromuscular block was achieved with vecuronium, followed by intubation with a left double lumen endobronchial tube. All patients received an extradural fentanyl bolus (1 μg kg^{-1}) followed by an infusion (1 μg kg^{-1} h^{-1}) during the study period. A pulmonary artery catheter was inserted in six patients from each group who consented to this additional monitoring. Ventilation was adjusted to maintain Pa_{CO_2} between 4.7 and 5.9 kPa (35–45 mm Hg). Intravenous fluid boluses were given to maintain mean arterial blood pressure within 20% of baseline. Blood gas and cardiovascular variables were measured at the end of each 30 min period of OLV. Statistical analysis was performed using Wilcoxon signed rank test for paired data and Mann–Whitney U test for unpaired data. For all tests, the level of significance was set at 5%.

Patient characteristics and preoperative data did not differ significantly between the two groups. There was no significant difference in any of the measured variables attributable to treatment order effect (group I *v* group II). There was a significant increase in heart rate (p_{sevo}<0.02; p_{iso}<0.01) and decrease in the mean arterial pressure (p_{sevo}<0.01; p_{iso}<0.01) during OLV with sevoflurane and isoflurane when compared to baseline values. None of the measured variables differed significantly between the treatment groups (sevoflurane *v* isoflurane) (table 2).

Table 2 Comparison of sevoflurane and isoflurane. Mean (SD)

	HR (min^{-1}) n=16	MAP (mm Hg) n=16	Pa_{O_2} (kPa) n=16	MPAP (mm Hg) n=12	CO (1 min) n=12	Sv_{O_2} (%)	Q/Q_t (%) n=12
Sevoflurane	82 (10.6)	75 (7.4)	21.3 (14.9)	23 (6)	6.3 (1.4)	76 (8)	43 (10)
Isoflurane	83 (10.4)	77 (9.3)	22.7 (13.6)	23 (7)	6.4 (1.8)	76 (8)	41 (10)

During OLV, the choice between sevoflurane and isoflurane does not significantly influence arterial oxygenation.

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Neutrophil activation and ischaemia–reperfusion syndrome in liver transplantation: evidence for

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We have previously shown release of arachidonic acid metabolites and increased expression of cytokines but not adhesion molecules following graft reperfusion in orthotopic liver transplantation (OLT).[1] In this study we aimed to determine whether subsequent neutrophil activation plays a part in haemodynamic instability and graft injury Blood samples were taken from 40 patients undergoing elective OLT at induction of anaesthesia 5 min before and 5 min and 1 h after graft reperfusion. No patient received preoperative immunosuppression. Monocyte intracellular calcium was measured as previously described.[2] Serum samples were frozen at −70°C and neutrophil elastase (α_1 proteinase inhibitor elastase complex) subsequently measured by EIA. Haemodynamic data were recorded at the same intraoperative time points. Postoperative liver function tests were measured on days 3 and 7. Results are expressed as median and interquartile range. Cardiac index rose from 5.1 (3.0 to 5.7) at induction to a peak 6.1 (3.5 to 7.4) following reperfusion (P<0.003). This was associated with a reduced SVRI Monocyte cytoplasmic calcium rose from 15.4 (7.0 to 25.5) to 20.5 (12.4 to 41.7) nmol l^{-1} (P<0.002). Neutrophil elastase rose progressively (fig 1). There was no correlation between elastase and monocyte intracellular calcium haemodynamic variables or postoperative liver function tests.

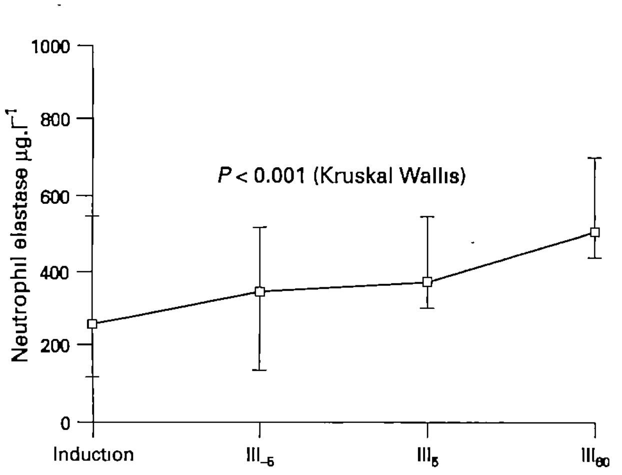

Figure 1 Change in neutrophil elastase.

In IRS, monocyte activation occurs secondary to intracellular calcium influx. Rising elastase levels suggest neutrophil activation. Monocyte intracellular calcium did not correlate with neutrophil elastase release. Neutrophil elastase did not correlate with any clinical end point. We have provided evidence for neutrophil activation but no evidence for its role in development of post-reperfusion injury in this population.

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Neutrophil activation following reperfusion in orthotopic liver transplantation: the argument against

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We have previously described activation of the arachidonic acid cascade, and cytokine release during ischaemia–reperfusion syndrome (IRS) in orthotopic liver transplantation (OLT).[1] Intracellular calcium in monocytes rises, suggesting cell activation.[2] Raised elastase suggests neutrophil activation, but failure to express E-selectin[1] is inconsistent with neutrophil adhesion and diapedesis. To investigate this hypothesis we looked at surface antigens on monocytes and neutrophils.

Nine consecutive patients undergoing elective OLT were studied No patient received preoperative immunosuppression. Blood samples were taken at induction of anaesthesia, 5 min before graft reperfusion, 5 min, 60 min, 6 h, and 24 h after reperfusion. Samples were taken from six healthy volunteers at equivalent time points. Surface antigens were labelled with fluorescent monoclonal antibodies and analysed by flow cytometry. Monocyte HLA-DR, CD14, CD11b, CD18, and neutrophil CD11b and CD18 (expressed as mean channel fluorescence, MCF) were measured. Results (median, range) were analysed by Friedman's analysis of variance (ANOVA).

Expression of CD antigens in OLT patients was lower at all times than in healthy controls. There was progressive reduction in monocyte HLA-DR expression (P=0.0007) and in CD14 expression (P=0.011). This contrasts with the steady state seen in control subjects. There was no change in expression of neutrophil adhesion molecules CD11b/CD18 (fig 2).

We have shown reduced expression of leucocyte CD antigens in OLT patients compared with healthy volunteers There is progressive reduction in monocyte CD14 and HLA-DR expression suggestive of monocyte activation. This does not appear to trigger neutrophil adhesion/diapedesis as shown by unchanged expression of CD11b/CD18

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Upper airway reactivity and upper respiratory tract infection: effect of nebulized lignocaine

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Patients with viral upper respiratory tract infections (URTI) have abnormally increased upper airway reflexes (UAR). This may lead to laryngospasm, bronchospasm, increased secretions, and hypoxaemia. Using inhaled ammonia as a chemical challenge, it has been shown that UAR sensitivity may be quantified [1] UAR sensitivity is greater in patients with symptomatic URTI for up to 9 d

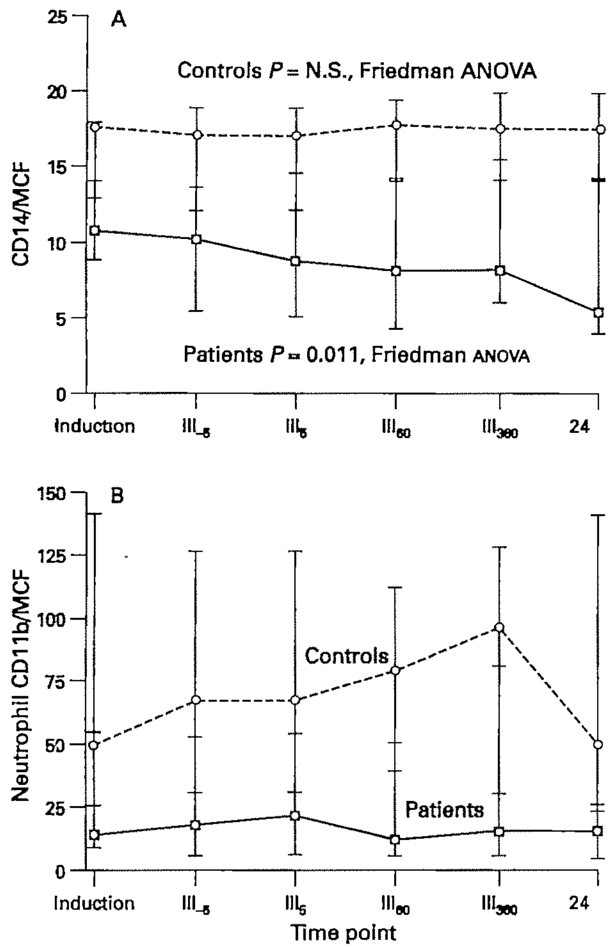

Figure 2 Changes in CD14/MCF (A) and neutrophil CD11b/MCF (B).

after the onset of symptoms.[2] It has also been shown (in healthy volunteers) that UAR sensitivity is reduced after nebulized lignocaine.[3] Viral URTI is a common preoperative finding, often leading to surgical cancellation. However, this may not always be possible. We aimed to examine the effect of nebulized lignocaine on UAR sensitivity in volunteers with symptomatic URTI, since any reduction in sensitivity may lessen the increased morbidity associated with anaesthesia in these patients.

Fifteen volunteers aged 22–43 years were recruited among colleagues. All were within the first 4 d of URTI, had symptoms in both the nose and throat, and felt malaise. UAR were assessed using a challenge of ammonia in inspired air to assess the threshold concentration (NH_3TR) producing a "glottic stop."[1] This is a reduction in inspiratory flow caused by brief adduction of the vocal cords. Baseline NH_3TR was determined. This was followed by a 4 ml solution of either lignocaine 4% or saline nebulized in air, and then a second determination of NH_3TR was made. After a 2 h gap the procedure was repeated with the alternative solution by nebulizer. Order of presentation was randomly assigned. The observer was blinded to which solution had been given.

NH_3TR was found to increase in all subjects following nebulized lignocaine (table 3).

Following a convalescence period of at least four weeks, with no return of symptoms in the preceding two weeks, NH_3TR was reassessed. It was found to be increased in all 15 subjects (878 (327 to 1620) ppm).

Table 3 Effect of lignocaine and saline on NH_3TR. All data shown as median (range) NH_3TR in parts per million. *P=0.0007, Wilcoxon

Experiment 1: Nebulized lignocaine		Experiment 2: Nebulized saline	
Baseline 1	Post-nebulizer	Baseline 2	Post-nebulizer
327 (76–878)	878 (251–1620)*	327 (76–1000)	327 (76–1000)

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Epidural pain relief in labour: relative potencies of bupivacaine and levobupivacaine

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Maternal deaths owing to intravenous injection of racemic bupivacaine have prompted the development of new local anaesthetics claimed to be less cardiotoxic.[1] Such claims cannot be evaluated before analgesic potency has been comparatively assessed. This study was undertaken to establish the relative potencies of racemic bupivacaine and its S-enantiomer, levobupivacaine, when used for extradural pain relief in labour, by comparing the minimum local analgesic concentrations (MLAC).[2]

Women in labour at less than 6 cm cervical dilatation were randomized to receive extradurally either racemic bupivacaine or levobupivacaine according to double blind sequential allocation. A lumbar extradural catheter was placed in an established and standardized manner. A first bolus of levobupivacaine or bupivacaine was given, diluted to 20 ml with 0.9% saline to a concentration determined by the response of the previous woman in that group according to up-down sequential allocation. The initial concentration was 0.07% wt/vol for both drugs. Pain was assessed with a 100 mm visual analogue pain score (VAPS), every 5 min up to 30 min. There were three possible outcomes: (1) *effective*—this required a VAPS of 10 mm or less at the height of a contraction, and directed a decrement of 0.01% wt/vol of local anaesthetic for the next woman in that group; (2) *ineffective*—a VAPS greater than 10 mm that fell to 10 mm or less following the administration of a rescue bolus of 15 ml bupivacaine 0.25% wt/vol; this directed an increment of 0.01% wt/vol of local anaesthetic for the next woman in that group; (3) *repeat*—when the rescue bolus failed to achieve a VAPS of 10 mm or less, the concentration was repeated for the next woman in that group.

There were no significant demographic differences between groups. MLAC was calculated using the formula of Dixon and Massey (table 4).

Table 4 Minimum of local anaesthetic concentrations (MLAC)

	MLAC (%w/v)	95% CI	MLAC (mmol litre^{-1})	95% CI
Racemic bupivacaine (HCl) n=30	0.08	0.055, 0.108	2.49	1.69, 3.32
Levobupivacaine (free base) n=30	0.083	0.065, 0.101	2.87	2.25, 3.49
Potency ratio L:B	0.98	0.67, 1.41	0.87	0.60, 1.25

The %wt/vol expression of each drug is different. A 2% difference in potency between the commercial preparations is unlikely to be of clinical relevance. Toxicological evidence should be evaluated in the light of a possible 13% potency difference in molar concentration.

This study was commissioned by Chiroscience.

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The cardiovascular response to tracheal extubation: effect of a remifentanil bolus

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Emergence from anaesthesia and tracheal extubation may be associated with increases in blood pressure, heart rate, catecholamines and myocardial ischaemia in susceptible individuals.[1 2] Methods to attenuate these changes may result in delayed recovery from anaesthesia. It has been shown that remifentanil attenuates changes in heart rate and blood pressure at tracheal intubation.[1] In view of its short duration of action, we investigated the effect of remifentanil on the cardiovascular response to extubation.

Forty females (aged 17 to 50 years, ASA 1–2) scheduled for elective day case laparoscopy were recruited. Each subject was randomized in a double blind fashion to receive either remifentanil or saline before extubation. All patients received a standard general anaesthetic comprising propofol, vecuronium, oxygen, nitrous oxide and isoflurane. Analgesia was provided with fentanyl 1.5 mg kg^{-1}, diclofenac 100 mg PR and bupivacaine 0.5% wound infiltration. At the end of surgery a bolus of remifentanil 1 µg kg^{-1} or saline was injected over 30 s and neostigmine and glycopyrrolate given. Mean arterial pressure (MAP) and heart rate (HR) were recorded at intervals of 60 s until 5 min after extubation. Quality of extubation, postoperative sedation and recovery time were also compared between groups.

Cardiovascular data are presented in table 5. There were no differences in age, weight, MAP, and HR before the start or end of surgery. There was a significant rise in MAP in the saline group at extubation, which was attenuated in the remifentanil group ($P<0.01$). MAP and HR were compared using MANOVA (paired and unpaired tests as appropriate). Mean (SEM) time to extubation was 7.2 (0.6) and 4.0 (0.5) min in the remifentanil and saline groups respectively ($P<0.001$), but there were no differences in quality of extubation, time to recovery from anaesthesia, or discharge from the recovery room (Mann–Whitney tests).

A bolus of remifentanil 1.0 µg kg^{-1} at the end of surgery attenuated the rise in MAP at emergence from anaesthesia and tracheal extubation but delayed the time at which extubation was possible.

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Table 5 Mean (SEM) mean blood pressure and heart rate at tracheal extubation. **$P<0.01$

Group	Pre-extubation	1 min post extubation	2 min post extubation	3 min post extubation	5 min post extubation
Remifentanil					
MAP	88.1 (2.8)	87 8 (3.2)	93.4 (2.7)	91.1 (2.7)	90.5 (2.0)
HR	73.3 (2.3)	75.7 (3.2)	80.3 (3.5)	80.1 (3.7)	74.9 (3.8)
Saline					
MAP	93.9 (3.0)	104 (3.0)**	102 (2.5)**	98.6 (3.6)**	92.0 (2.1)
HR	71.1 (2.5)	86.9 (3.4)	83.3 (3.5)	83.7 (2.8)	77.5 (3.4)

A qualitative investigation into the physical stability of polyethylene in isoflurane and sevoflurane

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Significant interactions between drugs and medical plastics occur when polyvinyl chloride is used in administration sets.[1] Absorption and permeation into plastics may affect dosage or composition; the converse (migration) results in plasticisers, stabilizers, or colourants entering the drug solution. Medical grade high density polyethylene has minimal interactions with glyceryl trinitrate and isosorbide.[2] Continuous direct injection of liquid volatile anaesthetic drugs into circle breathing systems using syringe drivers has been described,[1] but there have been no investigations of possible interactions between infusion system plastics and liquid volatile anaesthetic. We examined the stability of medical grade high and low density polyethylene in the presence of isoflurane and sevoflurane.

Six glass bottles containing 90 ml of either isoflurane or sevoflurane were prepared and stored at room temperature out of direct sunlight. A 20 g sample of both the high and low density polyethylene was added to two bottles, containing either isoflurane or sevoflurane, to give a total exposure time of one day, one week, or eight months. On day 250, the anaesthetic liquid and the polyethylene samples from all the bottles and control samples of isoflurane, sevoflurane and high and low density polyethylene were analysed by infrared absorption spectrometry using Fourier transform modulation (Perkin-Elmer FT-IR 100) to produce absorption spectra. All plastics and anaesthetic drugs were from the same batch. Comparison analysis of these spectra was performed and the presence of a new spectral trough/peak represented a change from the control spectrum, indicating absorption or migration (table 6).

Dr Renfrew was supported by a Clinical Research Fellowship from UNDAH Trust, Dundonald, Northern Ireland.

Table 6 Interaction between low/high density polyethylene and isoflurane and sevoflurane

	1 day exposure	7 days' exposure	250 days' exposure
Liquid sevoflurane	No difference	No difference	No difference
Liquid isoflurane	No difference	No difference	No difference
Low density/exposed to isoflurane	No difference	No difference	Additional spectra at 1100–1250 cm^{-1}
High density/exposed to isoflurane	No difference	No difference	Additional spectra at 1100–1250 cm^{-1}
Low density/exposed to sevoflurane	No difference	No difference	Additional spectra at 1100–1250 cm^{-1}
High density/exposed to sevoflurane	No difference	No difference	No difference

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Is tranexamic acid as effective as α2 antiplasmin at correcting coagulopathy in liver transplantation?

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We have previously shown fibrinolysis and blood loss in orthotopic liver transplantation (OLT) to be a function of the imbalance of α2 antiplasmin (α2AP) and tissue plasminogen activator (t-PA) arising during the anhepatic phase.[1] α2AP exerts its effects through lysine binding residues on plasmin and plasminogen, as does the antifibrinolytic drug tranexamic acid (TXA). α2AP is not available for therapeutic use in man. This *in vitro* study assesses the relative effectiveness of TXA and α2AP at correcting coagulopathy in OLT.

Samples of whole blood were taken from eight patients undergoing OLT, 30 min into the anhepatic phase, and 5 min after liver graft reperfusion. Samples were each divided into three aliquots. To these was added 0.3 ml TXA solution (final concentration 200 μg ml^{-1}), α2AP (70 μg ml^{-1}), or 0.3 ml saline control. These concentrations were chosen to approximate physiological/therapeutic circulating levels.[1,2] Coagulation was assayed by thromboelastography (TEG)[3] and fibrinolytic tendency by the dilute whole blood clot lysis time (DWBCLT).[4]

There were no differences in r, MA, or α angle between pre- and postreperfusion samples. Pooled DWBCLT and TEG data (mean and SEM) are summarized in table 7.

There is a trend towards less fibrinolysis when TXA or α2AP are used. Both agents bring about significant normalization of TEG variables. α2AP outperforms TXA with regard to clot strength (MA) whereas TXA results in more rapid clot propagation. These results support the rationale for prophylactic TXA use in OLT to correct pathological α2AP deficiency.

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Haemodynamic effects of Org 9487 in patients undergoing coronary artery surgery

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Org 9487 is a new aminosteroidal neuromuscular blocking agent with a rapid onset and possibility of early reversal.[1] In a preliminary study, administration of Org 9487 was associated with an increase in heart rate (HR).[2] The aim of the present study was to examine the haemodynamic effects of Org 9487 in patients undergoing coronary artery bypass grafting (CABG) surgery and compared these with vecuronium and saline (placebo).

Forty one patients with a left ventricular ejection fraction of ≥45% and on triple therapy of nitrates plus calcium entry and β receptor blocking drugs were enrolled into the study. Four patients were excluded owing to protocol violation, postponement of surgery, or technical difficulty. Premedication consisted of lorazepam, morphine, and hyoscine. Peripheral and central venous

Table 7 Pooled DWBCLT and TEG data. †All pairs significantly different. *On paired post-testing, $P<0.05$

DWBCLT	Control	TXA	α2AP	
<2 hr	7	3	4	
>2 hr	6	10	9	
P=NS, χ^2				
TEG variable	Control	TXA	α2AP	P (RMANOVA)
r/min	24.9 (8.2)	16.7 (5.6)	12.3 (2.3)	0.77
α angle/deg	23.7 (8.2)†	26.6 (7.1)†	25.3 (6.3)†	0.038
MA/mm	26.7 (6.6)*	32 (4.8)*	34.6 (6.1)*	0.009

Table 8 Main haemodynamic variables (mean (SD); *$P<0.05$ compared with baseline); a=12, b=11, c=6

		Baseline	+1 min	+3 min	+5 min	+10 min	+15 min
HR (beats min^{-1})	Org 9487	52 (9.0)	56 (9.3)*	60 (9.0)*	5 (8.2)*	58 (9.6)*	56 (8.2)*
	Vec	51 (11.7)	49 (11.6)*	50 (11.7)*	49 (11.8)	48 (10.5)*	48 (11.6)*^{b}
	Placebo	52 (8.4)	50 (5.4)	49 (5.4)*	49 (5.5)*	48 (5.9)*^{b}	50 (6.8)^{c}
MAP (mm Hg)	Org 9487	74 (15.6)	73 (16.5)	65 (14.4)*	66 (14.6)*	69 (14.0)*	69 (13.0)*
	Vec	79 (12.6)	78 (11.0)	79 (11.7)*	79 (10.9)	76 (11.4)	78 (13.4)^{b}
	Placebo	74 (12.0)	75 (9.0)	74 (8.2)	74 (8.3)	73 (7.7)^{b}	72 (7 0)^{c}
CO (litre min^{-1})	Org 9487	3.81 (0.86)	4.40 (1.13)*	4.44 (1.34)*	4.44 (1.43)*	4.28 (1.07)*	4.19 (0.91)
	Vec	4.34 (1.11)	4.25 (0.99)	4.18 (1.13)*	4.21 (1.04)	3.96 (0.79)	3.87 (0.83)^{b}
	Placebo	4.09 (0.58)	4.14 (0.55)	3.99 (0.62)	4.02 (0.69)	4.11 (0 46)^{b}	4.04 (0.50)^{c}
SVR (dyne s^{-1} cm^{-5})	Org 9487	1416 (251)	1241 (222)*	1125 (229)*	1127 (224)*	1192 (221)*	1238 (250)*
	Vec	1339 (334)	1352 (306)	1418 (368)*	1402 (313)	1417 (300)	1486 (361)^{b}
	Placebo	1297 (308)	1284 (263)	1330 (268)	1314 (283)	1265 (233)^{b}	1239 (270)^{c}

and radial artery cannulae and a pulmonary artery flotation catheter were inserted before induction of anaesthesia, which was with fentanyl 25–50 µg kg^{-1} and midazolam 2–5 mg. Tracheal intubation was carried out using suxamethonium 1.0 mg kg^{-1}. Ventilation was with an air-oxygen mixture (FIO_2=0.5). Following recovery from suxamethonium and with stable heart rate (HR) and arterial pressure, patients received Org 9487 1.5 mg kg^{-1} (n=12), vecuronium 0.1 mg kg^{-1} (n=13), or placebo 5 ml (n=12), as per the random allocation. HR, arterial pressure and cardiac output (CO) were measured immediately before study drug administration (baseline) and 1, 3, 5, 10, and where possible 15 min later. Other results were derived from these measurements. The data were subjected to ANOVA and Hochberg-Bonferroni post-tests.

Some results are given in table 8. Baseline measurements were not significantly different in the three groups. HR decreased slightly but significantly in the vecuronium and placebo groups; other changes were minimal in these groups. There was an increase in HR and a decrease in mean arterial pressure (MAP) in the Org 9487 group; these were significant, the maximum changes being +15% and +12% respectively for HR and MAP at 3 min. The increase in CO with Org 9487 was significant up to 10 min (maximum change +17%). There was a significant decrease in systemic vascular resistance throughout the study period (maximum decrease of 21%).

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Loss of heart rate variability in critically ill patients

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Gaudin *et al* showed that endotoxaemia caused a reduction in heart rate variability (HRV) in volunteers.[1] Based on the work of Pincus, showing that uncoupling of biological oscillators caused loss of variability,[2] it was suggested that breakdown of possible interorgan communications (uncoupling) was a feature of multiple organ dysfunction syndrome (MODS).[1] This hypothesis, if true, could have important applications. We believe that it may be possible to determine threshold values for HRV which could have diagnostic and prognostic significance. This study was done to examine whether loss of HRV could be demonstrated in high risk (unsedated) patients before MODS is established.

HRV was examined in seven unsedated, high risk patients admitted to an intensive care unit (mean modified APACHE score 14). The results were compared with HRV seen in seven volunteers from a surgical ward (mean modified APACHE score 5). All subjects were in sinus rhythm and continued to receive all prescribed medications. Resting ECG was sampled at 1 kHz using standard equipment (CED1902 and DAP800) and analysed with standard software (CED Spike2) and custom software incorporating Pincus's algorithm.[3] Ectopic beats were eliminated before analysis using the Taylor expansion method.[4] Time/frequency domain analyses and approximate entropy (ApEn) were used to quantify variability. ApEn was calculated with 750 data points and parameter values set at m=2 and r=0.2 × (population SD of RR interval) as suggested by Pincus. The results are shown in fig 3.

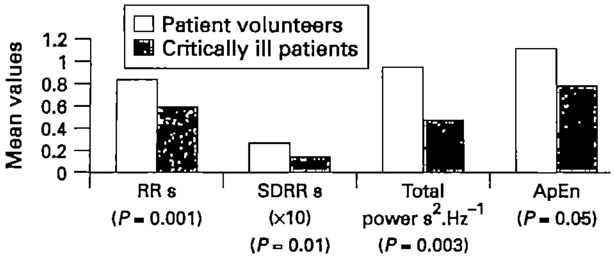

Figure 3 Comparison of parameters between critically ill patients and volunteers.

Significant reduction in heart rate variability (Student's two tailed t test) was seen in high risk patients and was demonstrated by all three parameters. The power within the individual frequency zones in the power spectrum, however, was variable, possibly owing to the range of clinical conditions and drug treatments involved in both groups. Calculated ApEn depends on the selected filter level, and more work is required before this statistic can have widespread clinical application. Our study supports the assertion that uncoupling of the cardiovascular system can be seen early in high risk patients before MODS becomes established.

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Evaluation of the mouthpiece for pre-oxygenation

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Pre-oxygenation is effective in preventing arterial desaturation during induction of anaesthesia.[1] Oxygraphy is established as a measure of pre-oxygenation.[2] This study originates from the clinical observation that many patients dislike face masks. The mouthpiece is used in clinical practice to give inhalational analgesia and nebulized drugs, but it is not known if its use for pre-oxygenation is effective.

This study has two parts—a volunteer study and a patient questionnaire. First, 20 healthy volunteers were sequentially allocated to receive 100% oxygen from each of three types of breathing apparatus—a face mask, a mouthpiece, and a mouthpiece used with a noseclip occluding the nares. The order in which these were first used was rotated. End expiratory oxygen (FE'_{O_2}) was recorded using a Datex capnomac after each 20 s interval during a 5 min period of tidal volume breathing, and again after each of five vital capacity breaths. A Mann–Whitney U test was used to analyse the FE'_{O_2} between the three sets of results at 180 and 300 s of tidal volume breathing, and after the fourth and fifth vital capacity breaths. Twenty patients received a questionnaire. All had experienced pre-oxygenation before undergoing uncomplicated surgery within the preceding few days. They were shown a Magill circuit with interchangeable black face mask and mouthpiece and asked if they had any preference. Their individual preferences were analysed using the binomial distribution of probabilities.

During tidal volume breathing, only 13 volunteers (subgroup A) were able to achieve an FE'_{O_2} above 90% using the mouthpiece. The other seven (subgroup B) required the additional use of a noseclip for the mouthpiece to be as effective as the face mask Conversely, during vital capacity breathing, the mouthpiece was equally effective with and without the noseclip, and achieved significantly better results than the face mask. Of the 20 patients questioned, 18 had a preference. Significantly more would have preferred to be pre-oxygenated with a mouthpiece (14/18) than a face mask (4/18) (P<0.05; CI 0.56 to 0.92) (table 9).

Patients prefer a mouthpiece to a black face mask for pre-oxygenation. The mouthpiece is safe for vital capacity pre-oxygenation. For tidal volume pre-oxygenation, the mouthpiece is not as effective as the face mask, unless the nares are mechanically occluded.

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Table 9 Final (5 min VT; 5th VC breath) mean end expiratory oxygen concentration (%). ***$P<0.001$; **$P<0.01$; *$P<0.05$; †NS (all compared with the face mask)

	All groups			Subgroup B		
	Face mask	Mouthpiece	Noseclip	Face mask	Mouthpiece	Noseclip
Tidal volume	91.4	70.3*	89.3†	90.7	60.1**	87.4†
Vital capacity	76	87***	86***	76	86**	83.4*

A comparison of the antibacterial activity of levobupivacaine versus bupivacaine: an *in vitro* study

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Infection in association with epidural anaesthesia is rare.[1] The well demonstrated antibacterial properties of local anaesthetics probably play a part in this low infection rate. Bupivacaine has antibacterial activity and this effect diminishes as the concentration is reduced.[2] Levobupivacaine, the S-enantiomer of bupivacaine, has been recently separated from the racemic compound for use as an alternative to bupivacaine. No data regarding its antibacterial activity exist; thus the aim of the study was to compare the antibacterial potencies of bupivacaine and levobupivacaine against those bacteria implicated in catheter associated infection.

Equal volumes of 0.125%, 0.25%, and 0.5% bupivacaine and levobupivacaine were made up by diluting with the bacterial growth medium Tryptone Soya Broth (TSB). Three bacteria were studied from the national collection of type cultures (NCTC): *Enterococcus faecalis* (NCTC 29212); *Staphylococcus aureus* (NCTC 6571); and *Staphylococcus epidermidis* (NCTC 7944). The anaesthetic/TSB solutions were inoculated with standardized suspensions of each bacterium and incubated for 24 h at 37 °C. For each bacterium, a standardized suspension with TSB alone acted as growth control and a suspension in saline enabled confirmation of the inoculum size. After incubation, samples from each mixture were plated onto blood agar, and colony counts recorded after a further period of incubation. The minimum concentration of local anaesthetic to give no bacterial growth was recorded as the minimum bactericidal concentration. One way analysis of variance and Dunnett's procedure were used to compare the mean colony counts with growth control counts.

No growth of any bacteria occurred in either 0.5% bupivacaine or 0.5% levobupivacaine (table 10). In 0.25% levobupivacaine the bacteria showed a small but significant decrease from TSB control. The colony counts were zero for all three bacteria in 0.25% bupivacaine. No differences from TSB control were seen for both the 0.125% solutions with the exception of *S aureus* in bupivacaine. The minimum bactericidal concentration of bupivacaine and levobupivacaine against all three bacteria was therefore 0.25% and 0.5%, respectively, for the *in vitro* conditions of this experiment.

Levobupivacaine was shown to have significant antibacterial activity. However, racemic bupivacaine has greater antibacterial activity, suggesting that the dextrobupivacaine isomer has a more potent antibacterial effect than the levobupivacaine isomer.

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Antioxidant potential of intravenous anaesthetic and analgesic agents

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Free radicals play a significant role in the pathogenesis of certain disease states Increased free radical mediated damage has been reported in the critically ill, along with decreased plasma antioxidant potential associated with increased mortality.[1] Propofol has *in vitro* antioxidant activity, forming stable non-toxic radicals in a similar manner to α tocopherol. The antioxidant potential of other anaesthetic agents is not known. The critically ill often receive infusions of anaesthetic and analgesic agents but it is not clear what contribution these agents may have to total antioxidant potential.

We used a spectrophotometric technique[2] to measure *in vitro* antioxidant potentials of six intravenous anaesthetic agents and two analgesic agents—propofol, thiopentone, methohexitone, etomidate, ketamine, midazolam, alfentanil, and fentanyl—at clinically relevant concentrations, against appropriate solvent blanks. Antioxidant potential was determined using quenching of the radical cation of 2,2′-azino-bis (3-ethylbenzo-thiaoline-6-sulphonic acid) (ABTS) formed by reaction with metmyoglobin in the presence of hydrogen peroxide. The assay was standardized using Trolox, a water soluble analogue of vitamin E, and results were expressed as Trolox equivalent antioxidant capacity (TEAC). Data represent results from six separate experiments and are expressed as median (range). Differences were assessed using Kruskal–Wallis analysis of variance or Mann–Whitney U test as appropriate.

Propofol showed significant dose dependent antioxidant potential ($P=0.0001$), across the concentration range studied. Intralipid, the solvent for propofol, had no effect. Even at the lowest concentration the antioxidant potential of propofol was twofold higher than that of normal plasma (antioxidant potential of 0.1 μg ml^{-1} propofol median 3.7 (3.6 to 4.0) TEAC compared with 2.0 (1.8 to 2.1) TEAC for normal plasma, $P=0.004$). All other anaesthetic agents tested also showed effects on antioxidant potential, compared with appropriate solvents. Thiopentone and methohexitone had significant negative effects (thiopentone $P=0.0033$; methohexitone $P=0.0013$). In contrast etomidate, ketamine and midazolam all had positive antioxidant potential ($P=0.003$, $P=0.0028$ and $P=0.0082$, respectively) but this was much less than that of normal plasma. Alfentanil also showed antioxidant potential ($P=0.0009$), again much less than plasma, but fentanyl was inactive ($P=0$ 45).

We have shown that propofol has significant antioxidant potential, twice that found in normal human plasma at concentrations similar to the circulating levels found at doses used for sedation and anaesthesia. The antioxidant potential of alfentanil, etomidate, ketamine and midazolam was much lower than that of normal plasma. The negative effect of the thiopentone and methohexitone suggests radical formation during the assay, probably related to the chemical structure of barbiturates. It is not known if the effects seen are common to other assays of antioxidant potential, which, although giving similar results for plasma,[3] may not be comparable for the study of drugs. Clearly further work is needed to elucidate the mechanisms involved.

Table 10 Mean log colony counts obtained for the three bacteria tested in levobupivacaine (L) and bupivacaine (B). NG=no growth, *=significantly less than TSB control ($P<0.05$)

	0.125%		0.25%		0.5%		Growth control	
	B	L	B	L	B	L	TSB broth	Saline
S. aureus	7.6*	7.9	NG*	7.65*	NG*	NG*	7.92	2.05
S. epidermidis	7.68	7.65	NG*	6.6*	NG*	NG*	7.72	2.03
Enterococcus faecalis	7.88	7.89	NG*	7.49	NG*	NG*	7.71	1.72

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Adenosine does not activate peripheral chemoreceptors in the rat

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Adenosine is commonly used in intensive therapy, principally for its antiarrhythmic action. It has been widely reported that adenosine increases minute ventilation in man and in animals.[1,2] Using intracarotid injections of adenosine in rats, we have found little immediate effect of adenosine on ventilation (unpublished data), suggesting that the peripheral chemoreceptors are not stimulated by adenosine. We studied the effect of adenosine and an $A2_A$ receptor analogue, CGS21680, on carotid chemoreceptor activity in rats, by recording from the carotid sinus nerve.

We studied male Wistar rats (340–440 g) which were anaesthetized with pentobarbitone 60 mg kg^{-1} intraperitoneally. We cannulated each rat's trachea, paralysed it with gallamine 8 mg, and ventilated its lungs with air using a tidal volume of 3 ml at a rate of 80 breaths min^{-1}. We cannulated the right femoral vein to allow intravenous injections, and both femoral arteries to allow measurement of blood pressure and heart rate and to permit arterial blood sampling. We cannulated the right external carotid artery and positioned the cannula so its tip lay about 5 mm below the carotid bifurcation. We identified the right carotid sinus nerve and placed it across two platinum electrodes: impulses in the nerve were amplified using a Neurolog system and were recorded onto magnetic tape. Incremental 3 mg of pentobarbitone were given hourly and blood gases were monitored. Intracarotid injections were given of adenosine 30–300 μg and CGS 21680 1–100 μg and, as controls, saline and sodium cyanide. Recordings were analysed using Spike II for Windows.

Figure 4 shows the response of carotid chemoreceptors to adenosine, CGS 21680 and saline.

We found no significant difference between the effect of either drug and the saline control (Kruskal–Wallis, $P>0.05$), suggesting that neither is effective in activating peripheral chemoreceptors in the rat.

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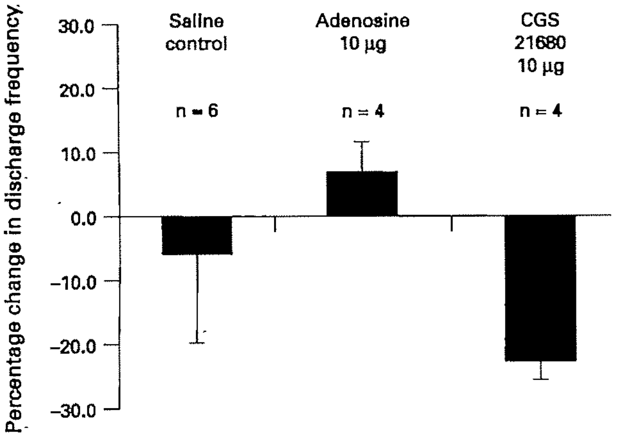

Figure 4 Percentage change in discharge frequency brought about by mid-range doses of adenosine and CGS 21680 and saline control (values are means, error bars=SEM).

A comparison of video imaging and cuff pressure change at the larynx

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Previous workers have measured the change in cuff pressure (CP) of an endotracheal tube (ETT) placed between the cords and shown that the onset of rocuronium action is significantly faster at the vocal cords than at the adductor pollicis.[1] We have shown, using video imaging of the larynx (VI) through a laryngeal mask airway (LMA), that the onset of rocuronium is significantly slower at the cords when compared with the hand.[1,2] The aim of this study was to compare the two techniques at 50% reduction in T1 at the adductor pollicis.

10 healthy patients (ASA 1 or 2) were recruited. Anaesthesia was induced and maintained with propofol supplemented with alfentanil and the lungs ventilated with 30% O_2 in N_2O A force transducer was attached to the right adductor pollicis and connected to a closed loop feedback system for administration of rocuronium. The recurrent laryngeal nerve was stimulated as described previously[1] with a train-of-four stimulus at 15 s intervals. The stimulus was applied to both sites simultaneously. The study was performed as follows: (1) LMA sited and baseline images of the cords recorded for 3 min at supramaximal current; (2) ETT (Mallinckrodt 7.5 mm) positioned and baseline CP (resting and maximum twitch height) recorded for a further 3 min; (3) administration of rocuronium started to a target of 50% of baseline T1 at the hand; (4) further CP recordings were made when 50% block at the hand was achieved; (5) if the resting CP changed from baseline, this was restored and further recordings made; (6) LMA resited and vocal cord images recorded at 50% block at the hand.

The results from the CP and VI recordings at the larynx were compared using Student's *t* test with Bonferroni correction and Bland–Altman plots.

The resting CP decreased from a baseline value of 21 (4) to 12 (5) mm Hg (mean (SD)) following administration of the relaxant ($P<0.0001$) (table 11).

Following administration of rocuronium, the resting pressure in the cuff of an ETT placed between the cords decreases. If the resting pressure is restored to the baseline value, the level of neuromuscular block at the larynx as assessed by video imaging is in agreement with that determined by cuff pressure measurement during 50% block at the hand.

We acknowledge financial support for this work from NHS Executive Trent and Nottingham Hospitals Special Trustees.

Table 11 *$P<0.0001$ when compared with measurements at reduced resting CP

Site monitored	% reduction in T1 mean (SD)	Bland–Altman (CP *v* VI) mean diff % block (2SD)
Hand, adductor pollicis	49.7 (1.4)	
Larynx, reduced resting CP	61.8 (17.6)	35.0 (37.9)
Larynx, restored resting CP	29.0 (13.2)*	2.2 (22.1)
Larynx, VI	26.6 (14.1)*	

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Nuclear factor κB activation in the critically ill

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The host response to sepsis and inflammation is mediated in part by low molecular weight proteins called cytokines. Nuclear factor κB (NFκB) is an intracellular transcription factor which regulates genes for several cytokines and adhesion molecules. NFκB allows rapid upregulation of cytokine production by being activated independently of *de novo* protein synthesis. Activation occurs in response to a variety of stimuli encountered in the critically ill, including endotoxin, TNFα and IL-1β, nitric oxide and reactive oxygen intermediates. Circulating concentrations of several cytokines and soluble adhesion molecules have been shown to be associated with both the development of multiorgan dysfunction and poor outcome. We assessed NFκB activation in critically ill patients on the intensive care unit.

Following ethics committee approval, mononuclear and polymorphonuclear leucocytes were isolated using density gradient centrifugation from seven critically ill intensive care patients at zero, 24 h, 48 h and 72 h. Nuclear proteins were extracted by hypotonic lysis, and NFκB activation was determined by electrophoretic mobility shift assay. Autoradiographs were quantified by densitometry as digital images, and expressed in terms of standardized protein loading, as mean counts mm^{-2}.

NFκB activation was shown in both cell types in all patients at each time point studied. In the four patients who survived, the level of both mononuclear cell and polymorphonuclear cell NFκB activation remained constant over the 72 h of the study, with a median NFκB value of below 1.9 counts. However, in the three patients who died, mononuclear cell NFκB activation increased markedly before death (fig 5). In all patients who died, NFκB activation was above 3.5 counts.

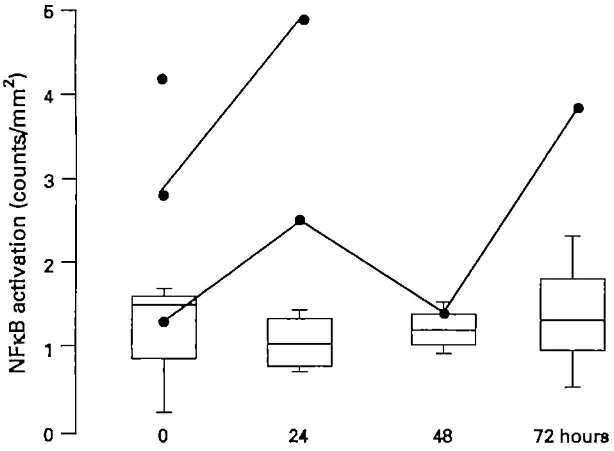

Figure 5 NFκB activation in mononuclear cells from critically ill patients. Boxes show median, 25th, and 75th centile and ranges for the four patients who survived. Circles are values for three patients who died.

We have shown that NFκB activation occurs in leucocytes from critically ill patients, and increases markedly in mononuclear cells from patients who die. Prevention of NFκB activation may be a novel therapeutic option in these patients.

TH1/TH2 cell ratios in spinal and general anaesthesia

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Surgical stress and anaesthesia suppress the immune system and may contribute to the development of postoperative infections and the spread of malignant disease. T helper lymphocytes play a major role in the immune response by controlling cell-mediated and humoral immunity. The type of immune response generated is determined by the differentiation of precursor T helper cells into Th1 or Th2 cells. Each cell subset secretes a particular array of cytokines which further augment the differentiation into that subset. Th1 cells produce interferon γ (IFNγ) and are responsible for cell-mediated immunity. Th2 cells produce interleukin-4 (IL-4) and are more effective in inducing humoral immunity. The relative balance of cytokine concentrations is altered by anaesthesia which may effect Th cell predominance and the nature of the subsequent immune response. We determined the relative effects of spinal and general anaesthesia on the Th1/Th2 cell ratio in patients undergoing transurethral resection of the prostate (TURP).

Mononuclear cells were isolated using density gradient centrifugation, from patients undergoing TURP—10 by general anaesthesia (propofol, isoflurane/N_2O/O_2) and nine by spinal anaesthesia (hypobaric 0.5% bupivacaine). Blood samples were obtained before anaesthesia, immediately after surgery, and again after 24 h. Cells were activated with ionomycin and phorbol ester in the presence of monensin, then fixed and stained with labelled anti-CD3 and anti-CD4 antibodies to select T helper cells. Cell membranes were then permeabilized with saponin and stained with labelled anti-IFNγ and anti-IL-4 and quantified by flow cytometry. The ratio of the percentage IFNγ positive (Th1 cells) to IL-4 positive (Th2 cells) was then calculated. Data are expressed as median (range) and differences assessed using Kruskal–Wallis analysis of variance or Mann–Whitney U test as appropriate.

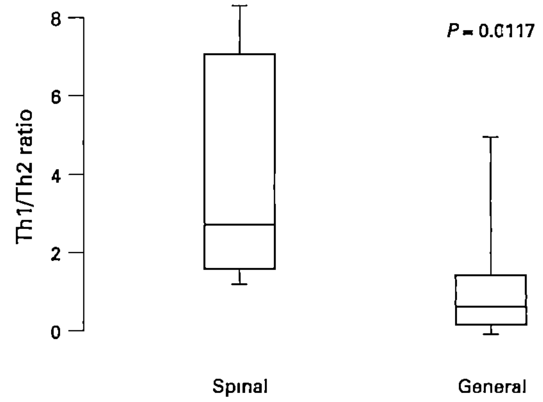

Figure 6 Th1/Th2 cell ratios at 24 hours in nine patients receiving spinal anaesthesia and 10 patients receiving general anaesthesia for TURP. Box and whisker plots show median, 25th, and 75th centiles and range as vertical lines. Data were compared using Mann–Whitney U test.

The Th1/Th2 ratios in patients receiving spinal anaesthesia increased over the three time points studied (*P*=0.029) but did not alter in those who had general anaesthesia (*P*=0.35). At 24 h, the Th1/Th2 ratio was significantly higher in the spinal group than that observed in patients undergoing general anaesthesia (*P*=0.0117, fig 6). This may suggest that spinal anaesthesia is more beneficial to the patient than general anaesthesia by maintaining Th1 cell numbers and thus promoting cellular immunity.

Differential effects of halothane on cardiac potassium channels

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K^+ channels are the most diverse class of ion channels in the heart. Phase 1 of the cardiac action potential is due to K^+ efflux via the transient outward current, I_{to}. This influences subsequent ion channels and action potential duration. Two K^+ α subunits, Kv1.4 and Kv4.2, cloned from cardiac tissue, may be responsible for I_{to}. Halothane attenuates K^+ channel currents.[1] Therefore, effects of halothane on these K^+ channels were studied.

Xenopus oocytes were collected and injected with mRNA encoding Kv1.4 or Kv4.2 using established procedures[2] and incubated before recording, using two-electrode voltage clamp. Oocytes were placed in standard solution (ND96). From a holding potential of −80 mV, pulses were applied from −80 mV to 60 mV, at a rate of 0.5 Hz. The protocol was repeated in ND96 solution containing 3% halothane. Data were collected and analysed using pClamp6 (Axon Instruments, USA) and Sigma Stat 2.0 (Jandel Scientific, Germany).

The Kv1.4 currents were not affected by application of halothane (*n*=6, fig 7A). Kv4.2 current was significantly depressed ((n=7), *P*<0.01, fig 7B). The decrease of Kv4.2 was reversible on wash-off of halothane.

We have shown that halothane has differential effects on cardiac K^+ channels. This may have implications in elucidating effects of halothane on cardiac cells.

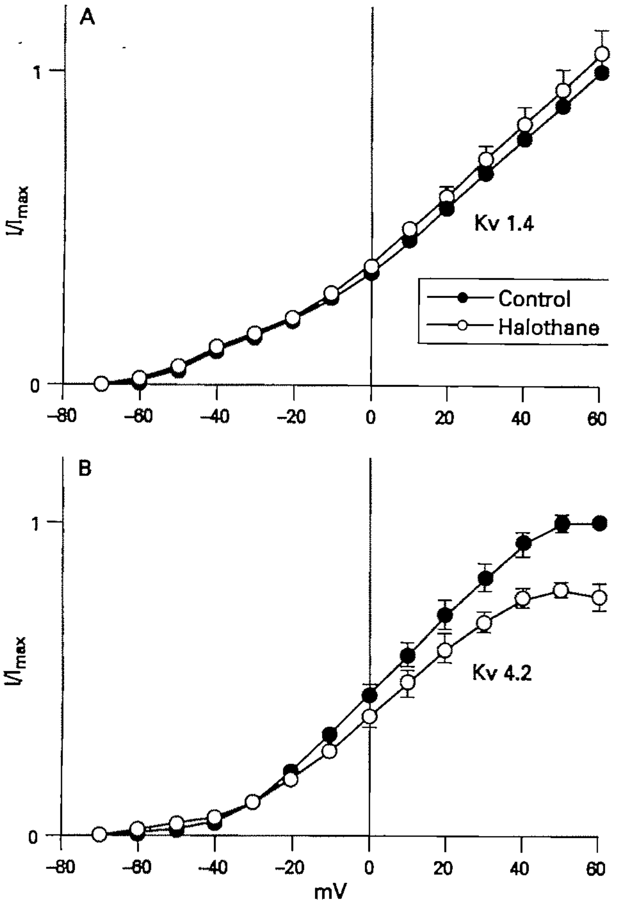

Figure 7 Current-voltage relationships under control conditions and in presence of halothane. Values are means; error bars=SEM.

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Pre-emptive glycopyrrolate and bradycardia during elective gynaecological laparoscopy

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During laparoscopy for gynaecological procedures, the combination of anaesthetic induction agents, Trendelenburg position and pneumoperitoneum can cause clinically significant haemodynamic alterations.[1] These may include bradycardia[2] and even asystolic cardiac arrest.[3]

Prompt treatment with atropine usually averts a potentially life threatening incident but can lead to unpleasant anticholinergic side effects such as urinary retention, blurred vision, and dry mouth. Glycopyrrolate, a quaternary amine muscarinic antagonist, does not cross the blood–brain barrier and is therefore not associated with these side effects.

In a prospective randomized, double blind clinical trial of 63 women undergoing elective gynaecological laparoscopy, preemptive glycopyrrolate 0.2 mg was given intravenously at induction of anaesthesia with fentanyl 1 μg kg^{-1}, propofol 2 mg kg^{-1} and mivacurium 0.15 mg kg^{-1} and maintenance was with O_2/NO_2 (50%) and isoflurane 1–1.5%. The effect on heart rate and blood pressure at 1 min intervals was noted in comparison to a control group given 0.9% saline.

Seven of 32 patients (21.6%) in the control group developed a bradycardia (taken as heart rate <50 beats min^{-1}), compared to three of 31 (9.6%) of the patients who received glycopyrrolate.

In this pilot study, pre-emptive glycopyrrolate 0.2 mg did not show a statistically significant increase in heart rate in a patient who had developed bradycardia during elective gynaecological laparoscopy.

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Effect of endotoxin on mechanical function and triacylglycerol metabolism in rat myocardium

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Systemic sepsis is associated with hypertriacylglycerolaemia, caused by raised very low density lipoprotein (VLDL). This is mediated by endotoxin and host inflammatory mediators, but the metabolic fate of the VLDL is unknown.

Livers from fasted control or endotoxin treated rats (0.1 mg kg^{-1} body weight) were perfused with [^{3}H]oleic acid for up to 18 h. The VLDL, separated by ultracentrifugation (d<1.006 g ml^{-1}), was used as a co-substrate (0.4 mM) with glucose (10 mM) for isolated perfused working hearts from control or endotoxin treated rats. VLDL-[^{3}H]TAG (triacylglycerol) oxidation was measured by the appearance of ^3H_2O. Hydraulic work = (coronary+aortic flow rates) × developed aortic pressure.

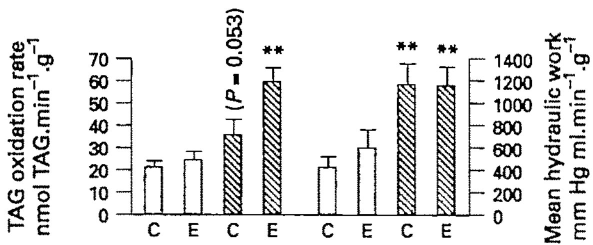

Figure 8 TAG oxidation rate and mean hydraulic work of control (C) and endotoxic (E) rat hearts perfused with either "control" or "endotoxic" VLDL. **$P<0.01$ *v* control heart and "control" VLDL. Mean±SEM; $n=6$ per group.

VLDL-TAG was found to be an efficient myocardial substrate and both forms of VLDL were associated with good cardiac mechanical function but "endotoxic" VLDL supported significantly more hydraulic work (fig 8). These data suggest that the hypertriacylglycerolaemia acts as an important source of fuel for the heart and may have a teleological role during sepsis. The increased oxidation rate of "endotoxic" VLDL-TAG may be caused by an alteration in the size or structure of the VLDL particle.[1] Compositional changes in VLDL synthesized by the liver and mediated by the inflammatory mediator cascade in sepsis may be a mechanism for redirecting substrates from non-essential depots to essential tissues, depending on the substrate preference of the target tissue lipoprotein lipase.

We thank the Wellcome Trust and *British Journal of Anaesthesia* for financial support.

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A proposed classification of stylo-hyoid ossification for anaesthetists

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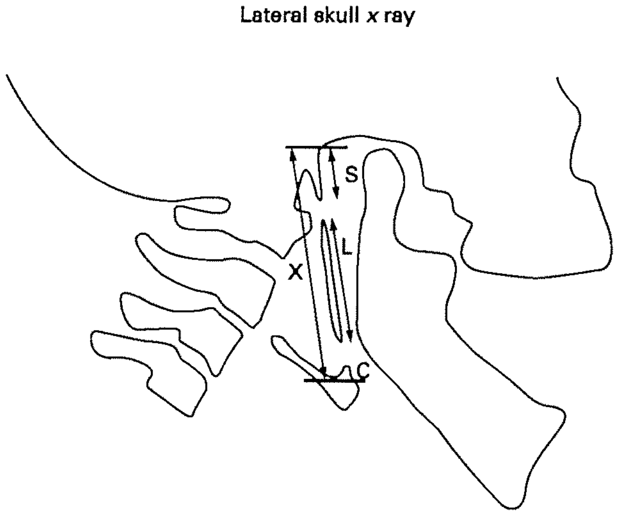
The styloid complex consists of the styloid process, lesser horn of the hyoid bone, and their interconnecting ligament. This ligament has the potential to ossify, and some individuals develop a rigid bony bar which may be interrupted along its length or be continuous. The aetiology of this transformation is unclear but may represent a normal aging process.[1] Ossification of the styloid ligaments is a rare cause of difficult intubation. Only six cases have been reported and description of the extent of ossification is vague,[2] but they seemed to all have complete bilateral ossification. Various classifications of ossification have been proposed, including patterns and shapes.[3] For anaesthetists, however, extent of ossification might be more important, though this has not yet been reported in normal subjects.

A retrospective analysis of departmental records for 48 subjects was undertaken. They had previously had straightforward ENT procedures (for example, tonsillectomy, septoplasty, etc). Before operation (when they were all reported as easy intubations) each had had a lateral *x* ray of the neck in a standardized intubating position,[4] with a dental prop to keep the mouth open 2.5 cm, and the lower jaw protruded maximally. From the neck *x* rays, the length of the stylohyoid complex was the distance from the most proximal part of the styloid process to the base of the lesser cornu of the hyoid (see fig 9). The styloid process length (tip to most proximal point seen) and any other areas of calcification were measured, added together, and expressed as a percentage of the whole complex length.



Key
X = total length of styloid complex
S = length of styloid process
L = length of ligament ossification
C = length of lesser cornu
Y = total ossification of complex = S + L + C
Y/X = % complex ossification

Figure 9 Calculation of ossification.

None of these patients was difficult to intubate and none had complete styloid hyoid calcification. Three had no ossification of the complex at all, while eight had one or more ossification segments in the ligament. The greatest overall ossification was 2% and more than 60% in just two others.

This is the first proposed classification of styloid ligament ossification for anaesthetists. Extensive stylohyoid ossification was not seen in these normal subjects. When this does occur, it is said to immobilize the larynx and this can be tested for by palpation.[2]

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Modelling the posterior pharyngeal wall

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A mathematical model for difficult intubation[1] describes intersection between an anterior airway line (upper incisors, I, to just above the laryngeal inlet, T) and a line, representing the mandible (between the two rami, J, to the internal midpoint of the symphysis, S). In difficulty the tongue is compressed by a "peardrop effect" which limits proximity of the blade tip to the larynx.[2] A photographic method provides an objective assessment of glottic view,[3] but when no view is obtained, there are no objective measures of difficulty. Modelling the posterior pharyngeal wall was considered the first step towards a suitable method.

Departmental records were reviewed for 20 patients who had a preoperative lateral *x* ray of the neck in a standardized intubating position with interincisor distance 25 mm.[1,4] Subsequently intubation was easy in all cases. These ITJS *x* ray coordinates, together with P and p1 to p8, were noted. P is where the posterior pharyngeal wall contacts the uppermost laryngeal structures and p8 is where it intersects with a tangent along the lower C2 body. p1 to p7 were points equidistant down from p8 to P. A computer printout was generated and checked against the original for accuracy. The coordinates were then corrected for radiological magnification.

Figure 10 shows 20 plots of I, P, and p1 to p8 with the I's coincident and IP's collinear. The posterior walls are either linear or reasonably approximated by a straight line The mean value for the angles IPp8 was 42.6° (SD 5.8°), IP was approximately equal to IT (limits of agreement, –0.45 to 1.22 cm) and the lengths JS and IP were significantly correlated ($P<0.001$).

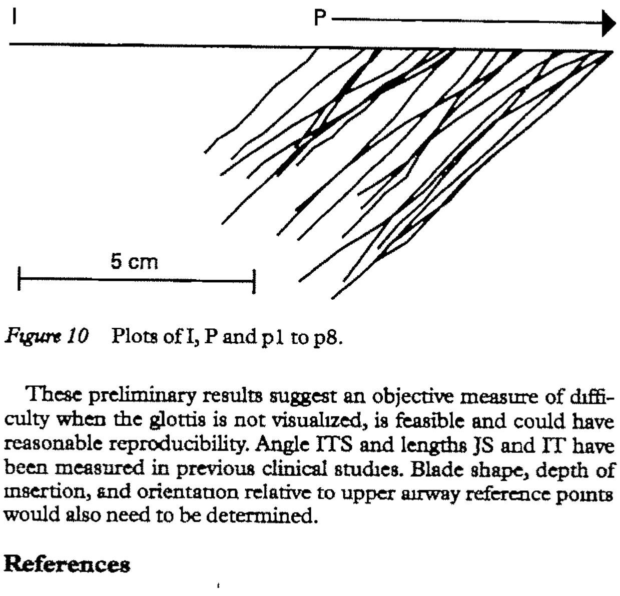

Figure 10 Plots of I, P and p1 to p8.

These preliminary results suggest an objective measure of difficulty when the glottis is not visualized, is feasible and could have reasonable reproducibility. Angle ITS and lengths JS and IT have been measured in previous clinical studies. Blade shape, depth of insertion, and orientation relative to upper airway reference points would also need to be determined.

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Using breathing system filters as oxygen delivery devices

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Laryngeal mask airways (LMA) are becoming increasingly popular as a method of providing an airway in ventilated and spontaneously breathing patients. The LMA may remain in situ when the patient is transferred to the recovery room. Breathing system filters are recommended for use during anaesthesia to prevent cross infection,[1] and also humidify the gases delivered to patients. A filter attached to an LMA can be used as an oxygen delivery system device by giving oxygen through the gas sampling port.[2] We compared the minimum $F\text{I}_{O_2}$ delivered in this way using two different filters with a T piece system incorporating a 40% oxygen injector. We used different flows of oxygen and different ventilatory conditions (tidal volume and frequency) delivered by a spontaneously breathing patient model.

Two breathing system filters, the Hygrobac S and the Sterivent (DAR, Mirandola, Italy), were used as oxygen delivery conduits and were compared with an oxygen delivery consisting of a 40% oxygen injector and a T piece with an attached 15 cm length of 22 mm corrugated tubing. The 40% oxygen injector is intended to be used with a flow of oxygen of 10 litre min^{-1}. Medical grade oxygen was administered at flows of 4, 7, and 10 litre min^{-1}. The patient model was set to deliver a sine wave flow with a tidal volume of either 0.5 or 0.75 litre at a frequency of 10, 15, or 20 min^{-1}.

The minimum $F\text{I}_{O_2}$ delivered by the T piece was around 0.32 under all test conditions. The minimum $F\text{I}_{O_2}$ delivered by the filters increased as the flow of oxygen was increased or as the frequency was reduced, and was greater than that delivered by the T piece at all ventilator conditions with a flow of oxygen of 7 or 10 litre min^{-1} (figure 11 illustrates results with a tidal volume of 0.5 litre).

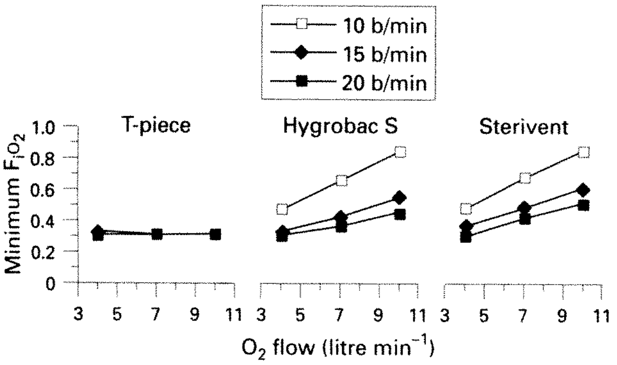

Figure 11 Min $F\text{I}_{O_2}$ as a function of O_2 flow.

A breathing system filter used as an oxygen delivery device provides high concentrations of oxygen with humidification and reduces cost by requiring less equipment. However, this oxygen delivery device has to be used with care to prevent the risk of barotrauma.[3]

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Postural stability and day surgery anaesthesia

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Previous studies of postural stability have assessed stability after thiopentone and methohexitone.[1 2] The Biodex balance system quantifies dynamic postural stability. We used this system to measure postural stability in patients undergoing day case anaesthesia with propofol and remifentanil for minor gynaecological procedures.

20 women (ASA I or II) undergoing hysteroscopy or suction termination of pregnancy were recruited. Anaesthesia consisted of a target controlled infusion of propofol (4–8 µg ml^{-1}), remifentanil (0.5 µg kg^{-1}) and atropine 0.6 mg intravenously. Patients breathed 30% oxygen in air spontaneously through a Bain circuit and laryngeal mask airway.

Stability was measured preoperatively, on first standing (recovery I), and just before discharge (recovery 2). The Biodex balance system is controlled by a microprocessor which allows setting of up to eight platform stability levels to challenge the patient's stability; level 8 is the most stable, level 1 the least. When testing patients, a cursor appears on the control panel of the balance system which the subject attempts to keep in the centre of a target as the platform becomes increasingly unstable beneath her.

Table 12 Median stability variables (95% confidence intervals)

	Group 1	Group 2A (cursor on)	Group 2B (cursor off)
Preoperative	1.90 (1.50, 2.45)	2.90 (1.80, 4.20)	3.60 (2.6, 5.50)
Recovery 1	2.00 (1.55, 2.55)	2.40 (1.70, 3.10)	3.50 (2.65, 4.75)
Recovery 2	1.65 (1.35, 2.50)	1.40 (1.30, 3.00)	3.30 (2.30, 4.35)

Stability was recorded as the stability index (SI) which is the variance of platform displacement in degrees from level. The first 10 subjects were tested for 2 min from level 8 to 4 (group 1). A second 10 subjects were tested for 2 min, 40 s from level 8 to 1 with the cursor both on (group 2A) and off (2B). Data were analysed by Mann–Whitney, Wilcoxon signed rank test and Student *t* test as appropriate.

Results are shown in table 12. There were no differences in age, body mass index (BMI), recovery times, or drug doses between the two groups. There were no differences in SI between group 1 and group 2A (P=0.09, Mann–Whitney). SI was significantly greater in group 2B compared with 2A at all times (P<0.025). In group 1, there was no difference in SI between preoperative and recovery tests. However, group 2A showed a significant difference in SI at all times which was absent in group 2B.

The lack of effect of anaesthesia on SI in group 1 may be caused by the short acting drugs used, or inadequate statistical power to detect a small difference. The effect of the cursor on SI is presumably due to visual feedback reinforcing the subjects' proprioceptive input and improving stability. The apparent improvement in SI with repeated testing in group 2A may be due to a learning curve, but if so this effect is negated in the absence of the cursor as shown in group 2B.

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POSTER PRESENTATIONS

Isoflurane inhibition of K^+ evoked [^{3}H] noradrenaline release from SH-SY5Y human neuroblastoma cells

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The cellular mechanisms of anaesthetic action are poorly understood. We have previously shown that halothane reduces K^+ evoked, but not carbachol evoked [^{3}H]noradrenaline (NA) release from SH-SY5Y cells.[1] K^+, but not carbachol, evoked NA release is dependent on extracellular Ca^{2+}, thus implicating Ca^{2+} entry in the action of halothane. In this study, we have examined the effects of isoflurane on K^+ stimulated [^{3}H]NA release from SH-SY5Y cells.

SH-SY5Y cells were maintained in supplemented minimum essential medium. Whole cell suspensions were incubated at 37°C with [^{3}H]NA (~40 nM) for 60 min in 3 ml Krebs HEPES buffer (pH 7.4), then washed in fresh buffer for 15 min ×3 before loading into a perfusion chamber.[1] The cells were perfused with Krebs buffer for 20 min. Following a 3 min basal perfusate fraction collection, a 100 mM K^+ buffer (S_1 stimulus) was applied for 3 min and a further 3 min collection performed. A second pulse of 100 mM K^+ (S_2 stimulus) was applied after 23 min and fractions collected. This procedure was performed for control and isoflurane treated cells. Isoflurane was delivered continuously from the start of the 20 min gap between S_1 and S_2 stimulations with a precalibrated Fluotec 3 vaporiser at 3, 4, and 5 Atm%, using humidified air as a carrier gas. [^{3}H]NA release was determined by scintillation spectrophotometry. The areas under the S_1 and S_2 stimulation curves were used to calculate an S_2/S_1 ratio for control and drug treated cells, from which the percentage inhibition was calculated. Data were analysed by Wilcoxon rank sum test and considered significant when $P<0.05$.

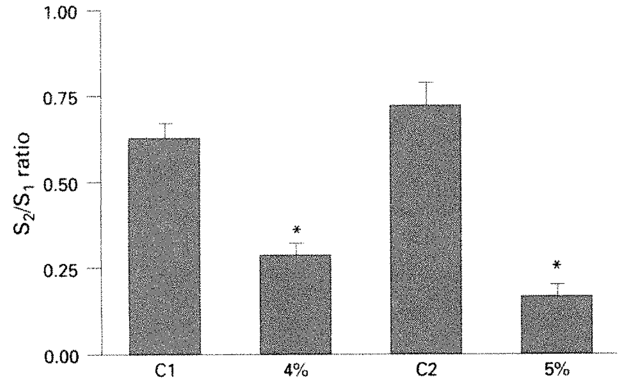

Figure 12 The effect of 4 and 5 Atm% isoflurane on [^{3}H]NA release. All S_2/S_1 ratio data are means, error bars=SEM. *$P<0.05$. C1 and C2 are paired air controls for 4 and 5 Atm% data respectively.

The results are shown in fig 12. K^+ produced a monophasic release of NA during S_1 and S_2 with a mean (SEM) S_2/S_1 ratio of 0.67 (0.17) (n=14). Isoflurane reduced the S_2/S_1 ratio at 5 and 4 Atm%. Preliminary data (n=3) with 3 Atm% produced a mean 49.7% inhibition.

These data support the hypothesis that isoflurane inhibits NA release through an action on voltage sensitive calcium channels.

Supported by a project grant from the *British Journal of Anaesthesia*.

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The effects of endomorphin-1 on cAMP formation and [Ca^{2+}]$_i$ in Chinese hamster ovary cells expressing recombinant μ-opioid receptors and SH-SY5Y cells

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Endomorphin-1 is a putative endogenous ligand for the μ-opioid receptor.[1] The aim of this study was to characterize the effect of endomorphin-1 on cyclic AMP formation and [Ca^{2+}]i in Chinese hamster ovary (CHO) cells expressing the recombinant rat μ-opioid receptor, and in SH-SY5Y cells expressing endogenous μ-opioid receptors.

CHO and SH-SY5Y cells were maintained in supplemented HAMS-F12 and minimum essential medium respectively. Cyclic AMP assays were carried out in whole cells in 0.3 ml assay volumes of Krebs–HEPES buffer (+0.5% BSA) in the presence of 1 mM 4-isobutyl-1-methylxanthine (IBMX), 1 mM forskolin, 30 μM amastatin, bestatin, phosphoramidon, and captopril (to prevent endomorphin breakdown), and endomorphin-1 (10^{-6} to 10^{-11} M) at 37°C. Cyclic AMP concentrations were measured by radio receptor assay as described previously.[2] [Ca^{2+}]$_i$ was measured fluorimetrically in fura-2 loaded whole cell suspensions in Krebs–HEPES buffer (+0.5% BSA) containing 30 μM amastatin, bestatin, phosphoramidon, and captopril at 37°C as described previously.[3] All data are mean (SEM), n=5.

Endomorphin-1 produced a dose dependent inhibition of forskolin stimulated cAMP formation in both CHO and SH-SY5Y cells with pEC_{50} values of 8.23 (0.31) (5.92 nM) and 7.98 (0.31) (10.47 nM) respectively and Imax values of 53(5)% and 32(4)% respectively. In CHO cells 1 μM endomorphin-1 produced a naloxone reversible, thapsigargin sensitive increase in [Ca^{2+}]$_i$ of 106 (28) nM. However, in SH-SY5Y cells 1 μM endomorphin-1 failed to cause a mobilization of [Ca^{2+}]$_i$.

These data show that in CHO cells endomorphin-1 causes activation of the recombinant μ-opioid receptor to inhibit cAMP formation and mobilize [Ca^{2+}]$_i$ from Ins(1,4,5)P_3 sensitive stores. In SH-SY5Y cells endomorphin-1 produces an inhibition of cAMP formation without increasing [Ca^{2+}]$_i$.

We would like to thank The Leicester Royal Infirmary NHS Trust for financial support.

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Effects of low dose dopexamine in hemihepatectomy patients

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Previous studies in animals and critically ill patients suggest that dopexamine causes an increase in splanchnic and renal blood flow owing to β_2 and dopamine receptor agonism.[1 2] The aim of this prospective, double blind randomized trial was to determine possible clinical benefits (hepatoprotective effects) of dopexamine in patients undergoing hemihepatectomy.

Twenty patients were randomly assigned to receive either dopexamine 0.5 μg kg^{-1} min^{-1} (DPX, n=10) or dopamine 2.5 μg kg^{-1} min^{-1} (DO, n=10). Infusions were started after induction of anaesthesia

Table 13 Haemodynamic data and splanchnic oxygenation (mean (SD)) for dopexamine (DPX, n=9) and dopamine (DO, n=10) groups. *$P\leq 0.05$

Variable		Baseline	Anhepatic	2 h postop	16 h postop
CI (litre min^{-1})	DO	4.3 (1.6)	3.7 (1.0)	3.7 (1.2)	3.7 (1.5)
	DPX	3.8 (1.8)	3.4 (1.0)	3.6 (0.7)	4.4 (0.8)
SVRI (dyn s cm^{-1} m^{-2})	DO	428 (233)	548 (260)	590 (233)	558 (206)
	DPX	384 (173)	554 (261)	599 (231)	432 (194)
SvO_2 (%)	DO	82 (3)	87 (5)	76 (14)	76 (5)
	DPX	78 (3)	83 (3)	80 (5)	77 (6)
$ShvO_2$ (%)	DO	67 (17)	63 (23)	75 (12)	70 (12)
	DPX	72 (16)	64 (23)	75 (16)	68 (15)
Arterial lactate (mmol litre^{-1})	DO	0.6 (0.2)	1.4 (0.9)	2.7 (1.8)	1.3 (0.5)
	DPX	0.8 (0.3)	2.0 (1.1)	3.1 (1.9)	1.7 (0.6)
Hepatic venous lactate (mmol litre^{-1})	DO	0.5 (0.2)	2.7 (1.5)	2.3 (1.7)	0.9 (0.5)
	DPX	0.7 (0.3)	2.8 (1.0)	2.7 (1.5)	1.5 (0.6)*
ME-GX (μg litre^{-1})	DO	151 (66)			62 (26)
	DPX	118 (52)			54 (23)

and continued postoperatively for 16 h. Radial and pulmonary artery and hepatic vein were catheterized. None of the patients received any other vasoactive drugs apart from DPX or DO during the study period. Systemic haemodynamics and oxygenation, hepatic venous haemoglobin oxygen saturation (Shvo$_2$), monoethylglycinxylid (ME-GX) formation from lignocaine, enzymatic indicators for hepatic cell damage, and recordings of hepatic synthesis performance were obtained on four occasions perioperatively. One patient had to be excluded for technical reasons. The data were compared between groups at 16 h postoperatively using the *t* test (table 13).

Low dose dopexamine, which significantly increases visceral blood flow in cardiac failure patients,[3] did not have a hepatoprotective effect superior to that of low dose dopexamine in hemihepatectomy patients.

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Genetic linkage analysis in malignant hyperthermia using a quantitative phenotype approach

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Genetic linkage analysis is a statistical technique that tests the association between a disease and a particular genetic marker within a family The measure of association is the lod score, a logarithmic scale in which +3 suggests linkage and −2 excludes it. Genetic linkage studies have established that malignant hyperthermia (MH) is a genetically heterogeneous disorder, the principal candidate locus being the ryanodine receptor gene (RYR1) on the long arm of chromosome 19. We have previously reported that, for some families, the lod score neither confirms nor excludes linkage to RYR1.[1] One explanation for this is misclassification of the phenotype of one or more individuals by the *in vitro* contracture tests (IVCT).

We have used a quantitative approach to phenotyping whereby the predictive probability of being susceptible to the disease is derived from the magnitude of the IVCT responses,[2] rather than simple allocation to one of three categories.[3] The predictive probabilities were used to allocate the phenotype and misclassification probability and the lod scores generated for chromosome 19q markers using the LINKAGE 5 4 computer program.

Our results (table 14) show that this method does not dramatically alter the lod scores. Of special interest is family 10, in which a single MH susceptible individual is recombinant for chromosome 19 markers. The shift of the lod score for this family away from the +3 value argues against phenotype misclassification being the cause of apparent discrepancy between standard IVCT and genetic "diagnosis." This further supports the possibility that the genetics of MH follows a complex model.[4] Standard IVCT interpretation remains the only safe way to diagnose or exclude MH.

Table 14 Lod scores for the RYR1 (or closest informative) marker using categorical or quantative phenotyping for malignant hyperthermia

Family	Marker	Lod score: categorical	Lod score: quantitative
03	RYR1	1.79	0.75
06	RYR1	1.35	0.5
07	RYR1	0.18	−0.2
09	RYR1	−0.13	0.158
10	RYR1	1.96	1.38
12	RYR1	−0 13	−0.01
22	D19S422	2.49	2.28
28	RYR1	1.48	0.088
45	D19S422	0.8	0.094
50	D19S422	0.99	−0.16

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Does high dose magnesium attenuate reperfusion rise in intracellular calcium in orthotopic liver transplantation?

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An increase in intracellular calcium is thought to be an important pathological event in the ischaemia–reperfusion syndrome (IRS). Several studies show this to be attenuated by pretreatment with magnesium.[1] We have previously described a rise in monocyte cytosolic calcium during human orthotopic liver transplantation (OLT), though this does not seem to be attenuated by low dose (10 mmol) magnesium.[2] We have therefore performed a pilot study to examine the effects of a high dose regimen.

12 consecutive patients undergoing elective orthotopic liver transplantation were randomized to receive 50 mmol magnesium or an equivalent volume of saline in a double blind fashion. Study drug was infused over a 20 minute period during the late anhepatic phase. Cardiac index (CI), mean arterial pressure, vascular resistance index (SVRI), and stroke volume index (SVI) were recorded at induction of anaesthesia, 5 min before graft reperfusion, and 5 min after reperfusion. Blood samples were taken for estimation of intracellular calcium as previously described.[2] Results are expressed as mean (SEM). Groups were compared by Student's *t* test.

Results are given in table 15. Intracellular calcium did not differ between groups at any time point. Haemodynamics were likewise similar at all time points, although stroke volume index showed a trend toward significance following reperfusion.

If magnesium attenuates intracellular calcium flux following reperfusion in this model, 4000 patients per group would be required to show this at the 5% level with 80% power The effect is probably not clinically significant. Stroke volume index may show a real difference in a larger study. Magnesium is unlikely to be important in modifying monocyte activation caused by IRS in human OLT.

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Table 15 Ca^{2+}, SVI and MAP in Magnesium and Placebo

	Magnesium	Placebo	*P* value
Ca$_i$ I nM	18.4 (7.8)	16.6 (4.5)	0.85
Ca$_i$ II nM	12.2 (5.3)	20.3 (5.7)	0.33
Ca$_i$ III nM	19.4 (3.9)	18.9 (3.2)	0.93
SVI I ml/m^2	66.4 (2.2)	51.3 (4.7)	0.02
SVI II ml/m^2	43.9 (1 9)	53.5 (7.1)	0.24
SVI III ml/m^2	88.5 (13.1)	62.2 (6.7)	0.08
MAP I mm Hg	79.5 (5.8)	78.5 (6.9)	0.91
MAP II mm Hg	71 (5.1)	82 (5 9)	0.18
MAP III mm Hg	83.3 (10.7)	67 3 (2 2)	0.23

Globe dimensions as a risk factor for penetrating ocular injury during peribulbar anaesthesia

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Penetrating ocular injury is a rare but serious complication of ocular anaesthesia,[1] and the risk may be increased in large eyes that are axially myopic. Previous studies have shown the increased risks in eyes with posterior staphyloma,[2] but increased equatorial dimensions could also be a risk factor during peribulbar anaesthesia using the medial approach. This study identifies the range of horizontal equatorial dimensions in axially myopic eyes using B scan echography.

Fifty patients (100 eyes) with axial myopia underwent B scan echography, and three measurements of axial length and equatorial horizontal width were made from each eye. The presence or absence of posterior staphyloma was also noted. The axial lengths were grouped into five ranges of 20 eyes: 23–25 mm, 25.1–27 mm, 27.1–9 mm, 29.1–31 mm, and >31 mm, and the group mean ratio of equatorial horizontal width/axial length (EHW/AL) was calculated for each range.

The mean EHW/AL ratios for each group were: 0.98 (23–25 mm), 0.94 (25.1–27 mm), 0.91 (27.1–29 mm), 0.3 (29.1–31 mm), and 0.79 (>31 mm). The largest EHW recorded was 27.3 mm in an eye with the largest AL of 34.1 mm (fig 13). Posterior staphyloma occurred in 60% of eyes with an AL>31 mm, compared with 35% of eyes with an AL of 29.1–31 mm and 0%<27 mm.

The measurements show that the increase in EHW is disproportional to increasing AL such that even in eyes with extreme axial myopia (>33 mm) the horizontal width is only 2 mm larger than an eye with an AL of 25 mm. This would indicate that the risk of penetrating ocular injury owing to increased equatorial horizontal width in axially myopic eyes is low when the medial canthal approach is used for peribulbar injection. However, the incidence of posterior staphyloma in eyes >29 mm is high and therefore we recommend that B scan echography be performed on eyes >29 mm to look for posterior staphyloma in order to validate biometry measurements, and to warn of potential risks of retrobulbar injection

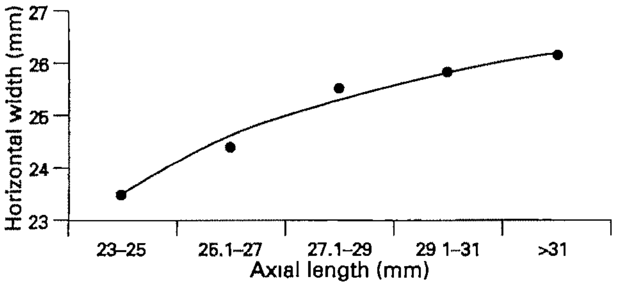

Figure 13 Relation between axial length and horizontal width (group means).

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Assessment of the 50 ml syringe as a simple training aid in the application of cricoid pressure

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The initial work on cricoid pressure stated that moderate and firm pressures were appropriate.[1] Since then, other workers[2] have sought to quantify the forces required. More recently, forces of 20, 30, and 40 newtons have been recommended at different stages during application of cricoid pressure.[3] Mechanical devices have been developed to accurately determine these forces during application,[4] but they are not in daily use. We have developed a simple training aid, using a capped air filled 50 ml syringe, which reproduces 20, 30, and 40 N.

We used 160 syringes, of four different types, to ascertain brand and intersyringe variation. A test rig was constructed of plaster of Paris and heat moulded plastic. The plaster of Paris mould held the air filled syringes vertically. The heat moulded plastic held lead shot which acted as weight to produce the appropriate force when placed on the plunger. The point to which each plunger fell from 50 ml was rounded to the nearest whole number and then recorded. After removal from the stand, the plunger was depressed under water to confirm the absence of air leak

The results for the series of experiments are shown in the table 16.

Table 16 Syringe plunger travel. Data shown are mean (SD) in ml, n=40

	20 N	30 N	40 N
Plastipak (B-D)	37.4 (0.5)	32.9 (0.1)	30.0 (0.2)
Omnifix (Braun)	38.0 (0.1)	33.5 (0.5)	30.4 (0.5)
OPS (Braun)	38.4 (0.5)	33.8 (0.4)	30.9 (0.4)
Sherwood	37.9 (0.6)	33.6 (0.5)	30.3 (0.5)

In conclusion, this shows a simple, reproducible method of demonstrating the recommended forces required for effective cricoid pressure.

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Pancuronium reverses methacholine inhibition of cAMP formation in Chinese hamster ovary cells expressing recombinant human muscarinic m2 receptors (CHOm2)

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Pancuronium has been implicated as the cause of tachycardia [1,2] In a previous study we reported that pancuronium displaced the muscarinic receptor radioligand from recombinant human muscarinic m2 receptors.[3] Muscarinic m2 receptors inhibit the formation of cAMP when activated by an appropriate agonist (for example, methacholine) and this inhibition is used as an index of receptor activation. In this study we examined the effects of pancuronium on methacholine mediated inhibition of cAMP formation in CHOm2 cells.

All studies were performed in whole cells in 0.3 ml of Krebs/HEPES buffer pH 7.4 supplemented with 4-isobutyl-1-methylxanthine (1 mM) and forskolin (1 μM). Cells were incubated for 15 min in the absence and presence of 300 nM pancuronium and methacholine (10^{-8} to 10^{-2} M) for 15 min. Reactions were terminated with 10 M HCl, neutralized with 10 M NaOH and 1 M Tris, pH 7.4, and cAMP was measured using a radioreceptor mass assay.[4]

Results are shown in fig 14. Methacholine inhibited forskolin stimulated cAMP formation with an estimated IC_{50} (half maximum inhibition) of 1.13 μM. The response at 100 μM was reversed by the muscarinic antagonist atropine. Pancuronium alone at 300 nM did not affect forskolin stimulated cAMP formation but shifted the methacholine dose–response curve 1051-fold to the right (IC_{50} 1192 μM).

These data suggest that pancuronium may be a competitive muscarinic antagonist and that this action at the m2 receptor in the heart may contribute to the tachycardia seen clinically.

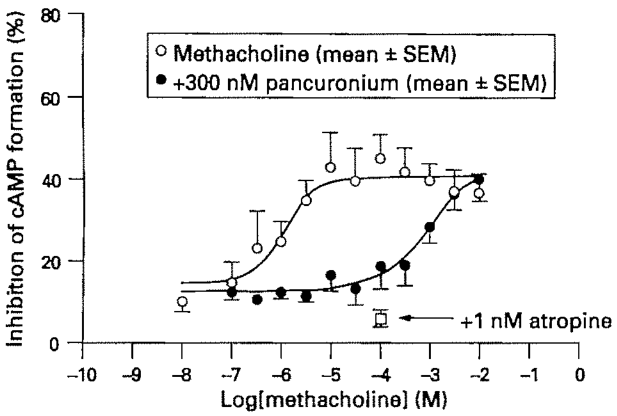

Figure 14 Effects of pancuronium on methacholine (METH) inhibition of cAMP formation.

TMC holds a University of Leicester PhD studentship. We thank Dr NJM Buckley (UCL, London) for providing CHOm2 cells.

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British Journal of Anaesthesia 1998; **81**: 294–300

CORRESPONDENCE

A role for presynaptic NMDA receptors in central sensitization in the spinal cord dorsal horn?

Editor,—Buerkle and colleagues report that intrathecal administration of remifentanil in rats that had received intraplantar formalin could wholly abolish nociceptive behaviour during phase 1 of the formalin test but was associated with only partial inhibition of glutamate release as measured by microdialysis.[1] Intraplantar injection of formalin results in a biphasic behavioural response, the second phase of which is considered to represent NMDA receptor-mediated central sensitization.[2 3] Phase 1 is characterized by paw flinching and licking corresponding to an acute barrage of small primary afferent fibre discharge and is followed, after a brief quiescent period, by a more protracted phase 2 period of similar behaviour associated with a lower level of tonic afferent activity.[4] Buerkle and colleagues contend that "supramaximal doses of intrathecal remifentanil sufficient to inhibit phase 1 behaviour still permit sufficient glutamate release to permit spinal facilitation" via presumed activation of a post-synaptic NMDA receptor during phase 1. Their data merit further discussion in the light of recent anatomical and functional demonstrations of presynaptic NMDA receptors in the spinal cord dorsal horn.[5 6]

The spinal action of remifentanil is mediated by μ-opioid receptors at both pre and postsynaptic loci within the dorsal horn, and as shown in this and previous studies,[3] opioid administration can abolish both phase 1 and phase 2 of the formalin test. However, where opioid effects are limited purely to phase 1 by intrathecal naloxone[7 8] or by the use of remifentanil,[1 9] only a partial suppression or delay of phase 2 behaviour has been reported despite abolition of the phase 1 behavioural response. Therefore, sensitization still occurs during phase 1 of the formalin test, and crucially, such sensitization may occur despite electrophysiological evidence indicating that opioid suppression of dorsal horn neurone firing during phase 1 may be virtually complete.[10] This "remifentanil-resistant" component of central sensitization of the current study was considered by Buerkle and colleagues to be a consequence of incomplete opioid-mediated inhibition of glutamate release from primary afferent or interneurone nerve terminals during phase 1, similar to that reported previously with systemic morphine.[11]

If the initiation of central sensitization underlying phase 2 of the formalin test involves postsynaptic NMDA receptor activation, it would be expected to require sustained depolarization of nociceptive neurones in the dorsal horn.[12] How can this be reconciled with the behavioural evidence of suppression of postsynaptic activity in this and other studies, and electrophysiological evidence of suppression of dorsal horn neuronal activation during phase 1 of the formalin test?[10 13]

Functional presynaptic NMDA receptors which potentiate the release of C-fibre primary afferent transmitters have been recently identified within the dorsal horn.[5 6] It may be hypothesized that the enhanced release of glutamate during phase 1 demonstrated by Buerkle and colleagues may activate such presynaptic receptors which are depolarized by virtue of phase 1 afferent activity. This activation of presynaptic NMDA receptors would initiate a long-lasting Ca^{2+}-mediated enhancement of primary afferent transmitter release and increase the gain of C-fibre synaptic transmission in the dorsal horn during phase 2. Fundamentally, presynaptic sensitization could occur despite opioid suppression of postsynaptic neuronal activity and would only become manifest behaviourally after opioid suppression of postsynaptic neuronal activity within the dorsal horn was removed.

Support for this hypothesis remains circumstantial in the absence of a selective antagonist of presynaptic NMDA receptors. However:

1. (1) Yashpal and colleagues report that intrathecal lignocaine given after phase 1 of the formalin test suppressed Fos expression in the dorsal horn but did not suppress nociceptive behaviour in phase 2.[14] Their data indicate that behavioural evidence of central sensitization persists despite suppression of an index of postsynaptic neuronal activation—again implicating a possible presynaptic component of sensitization.
2. (2) There is evidence that presynaptic NMDA receptors may differ structurally from postsynaptic NMDA receptors and be insensitive to polyamines.[15 16] Polyamines such as spermine which act as allosteric modulators of NMDA receptor function[17] are not analgesic in the formalin test when administered intrathecally[18] which may reflect lack of inhibition of presynaptic NMDA receptor function.

Thus central sensitization may occur via NMDA receptors on C-fibre primary afferent terminals despite effective block of postsynaptic responses by opioids. Such a possibility of a previously unrecognized component of spinal sensitization reinforces our previously expressed view[19] that conventional anaesthetics or analgesics (including μ-opioids) do not adequately inhibit the longer term consequences of painful stimulation.

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Editor,—We appreciate the comments about our study on the intrathecal injection of remifentanil, which inhibited the nociceptive behavioural responses evoked by formalin administration into the hind paw of the rat, but did not abolish the concomitant glutamate release at the spinal cord level, as assessed by the *in vivo* spinal microdialysis of cerebrospinal fluid in this model.[1] The initial response of the formalin test (phase 1) is caused by activation of peripheral nociceptors and is followed by a second phase attributed to ongoing activity in primary afferents and increased sensitivity of the dorsal horn neurones.[2,3] The latter effect is thought to result from glutamate-mediated N-methyl-D-aspartate receptor activation. Glutamate has been shown to be the major excitatory amino acid neurotransmitter in the central nervous system, playing a key role in central sensitization and spinal pain transduction mechanisms.[4] We agree that the initiation of central sensitization may also involve presynaptic NMDA-receptor activation, as was suggested by Liu and colleagues.[5,6] Thus the observed effects may be caused by a presynaptic sensitization, which becomes behaviourally apparent because of the short-lasting effects of the esterase-metabolized, ultra-short acting μ-opioid remifentanil or, which might be caused by the distinct differences in the temporal activation of pre- and postsynaptic NMDA-receptors. This hypothesis may be further supported by studies from Taylor and colleagues[7] and Abbadie and colleagues,[8] who reported that central sensitization mechanisms during phase 1 do not influence the magnitude of phase 2 after systemic delivery of remifentanil and that there exist regional differences of c-fos activation within the spinal cord laminae during complete suppression of phase 1 behaviour by remifentanil. In conclusion, we contend that in lieu of circumstantial evidence for the role of presynaptic NMDA receptors in central sensitization processes, further studies elucidating the role of pre- versus postsynaptic NMDA activation for central sensitization are warranted.

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Morbidity after day-case tonsillectomy in children

Editor,—Splinter and Rhine[1] quote an incidence of vomiting after day-case tonsillectomy in children of 40%, despite antiemetic treatment. Their comment that this is unacceptably high is indeed true. I believe this has more to do with the anaesthetic technique than the surgical procedure itself. The incidence of nausea and vomiting after day-case tonsillectomy in 280 children in Salisbury, is under 5%. On a recent telephone questionnaire, carried out the day after surgery, the score, on a scale of 1–10 as recorded by parents, was a mean of 0.9 for nausea. The anaesthetic procedure adopted for this surgery involves propofol or sevoflurane induction, the insertion of a laryngeal mask, spontaneous ventilation with enflurane and ondansetron 0.1 mg given i.v after induction. Analgesia is provided with morphine and non-steroidal analgesics. Patients are encouraged to drink up to three hours before surgery and as soon as possible afterwards, usually within an hour. I.v. fluids are not administered.

I wonder if the very high incidence of vomiting often quoted[2] is partly because of laryngeal intubation. Williams and Bailey studied the incidence of tracheal soiling by blood after intubation compared with a laryngeal mask airway for tonsillectomy.[3] Over 50% of children whose tracheas had been intubated had blood in their lower airway compared with none in the laryngeal mask airway group. I would suggest that blood can just as easily pass into the stomach as into the trachea during tonsillectomy, when the airway is maintained with a tracheal tube. In contrast, a laryngeal mask will provide substantial protection by obtunding the oesophagus. I suspect that it is the swallowed blood that gives rise to the nausea and vomiting. I also believe that the use of halothane and intermittent positive pressure ventilation does little to reduce the incidence of nausea and vomiting in this group of patients.

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Editor,—Thank you for giving us the opportunity to respond to Dr Church's letter.

The specific aetiology of vomiting after tonsillectomy is unknown and is presumably multifactorial. Factors known to contribute are the anaesthetic agents used, opioid administration, surgical technique and perioperative fluid management.

Dr Church reports an incidence of nausea and vomiting after day case tonsillectomy of less than 5%. To the best of our knowledge, a reported incidence of less than 40% is unusual if a prophylactic antiemetic has not been used. It is difficult to explain this large difference as the anaesthetic technique described by Dr Church is not significantly different from that used by ourselves and others who have reported on this problem. The differences reported by Dr Church are the routine use of a laryngeal mask airway, the non-administration of perioperative intravenous fluids, and the use of enflurane. Swallowed blood has always been known to be a significant contributing factor to postoperative vomiting following tonsillectomy. This becomes a significant factor immediately following surgery, when children usually swallow any blood present in the pharynx. The use of a laryngeal mask is obviously not a factor during the postoperative period. The hydration of patients has been shown to reduce the incidence of nausea and vomiting significantly during strabismus surgery, another procedure with significant nausea and vomiting postoperatively. It is difficult to perceive how its omission during tonsillectomy could contribute to reduction in the incidence of nausea and vomiting.

The incidence of nausea and vomiting following the use of halothane when compared to enflurane is, to the best of our knowledge, similar (i.e. approximately 15%–20%).

Given that nausea and vomiting following day case tonsillectomy are potentially serious problems, we would suggest that Dr Church's technique should be investigated under controlled conditions and the results reported.

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Differential effects of nitrous oxide and propofol on myogenic motor-evoked responses

Editor,—Ubags and colleagues[1] have made a further advance in the search for suitable anaesthesia techniques to permit motor-evoked potential monitoring during spinal surgery, by confirming the benefit of double over single-pulse stimulation. Despite that, responses were abolished by propofol in 2 of 12 patients who then required anaesthesia consisting only of sufentanil and 50% nitrous oxide with a neuromuscular blocking drug. The apparent absence of recall in their series will not entirely reassure many anaesthetists who would worry about awareness using this technique.

We would like to draw their attention to our study of transcranial single-pulse magnetic motor-evoked potentials in which anaesthesia was ensured by a methohexital infusion at up to 100 µg kg^{-1} min^{-1}.[2] Since that study was completed, the method has been simplified by the omission of ketamine and the inspired nitrous oxide concentration is usually maintained at around 0.25%. Eight patients have been monitored successfully with methohexital and alfentanil infusions, and a further four with methohexital and remifentanil at 1 µg kg^{-1} min^{-1}, which allows for awakening within 20 min of stopping the infusions.

The transcranial magnetic motor-evoked potential (tibialis anterior) after spinal column injury varies, depending upon the degree of neurological compromise, but typically lies within the range 10–300 mcV under methohexital/remifentanil anaesthesia. Even better responses would be obtained using this technique with a double-pulse magnetic or electrical stimulus.

The authors omitted mention of premedication in their patients so it is worth emphasizing that a hypnotic agent such as a benzodiazepine is best avoided for motor-evoked potentials.

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Editor,—We thank Dr Watt and colleagues for their interest in our paper. The authors state that benzodiazepines should be avoided when motor-evoked potential monitoring is indicated. We feel the use of a benzodiazepine premedication is necessary to reduce the likelihood of awareness, especially when a nitrous oxide/opioid anaesthetic technique is used. All our patients received diazepam 10 mg orally, 1 h before surgery. We accidentally omitted mention of premedication in our paper.

The authors' success with motor-evoked potential monitoring during anaesthesia with methohexital and very low concentrations of nitrous oxide is certainly promising. It is another indicator that tc-MEP monitoring to single transcranial stimuli is possible, provided that special anaesthetic regimens are used. However, the application of multi-pulse stimulation paradigms obviates the need to avoid standard anaesthetic drugs. Multi-pulse stimulation has been shown to enable tc-MEP monitoring during propofol/opioid anaesthesia[1,2] and isoflurane anaesthesia.[3] Recently, specifically designed multi-pulse stimulators, capable of delivering up to four (magnetic) or 10 (electrical) successive transcranial stimuli have become commercially available. We believe that the introduction of these stimulators into clinical practice will result in a more widespread acceptance of motor-evoked potential monitoring.

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Anaesthesia for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome

Editor,—We read with interest the article of Sammut and Paes[1] describing the management of a patient with Eisenmenger's syndrome for laparoscopic cholecystectomy and would like to make the following comments.

The physiological changes that occur with laparoscopy need to be considered carefully in these patients. The balance between pulmonary and systemic vascular resistance is critical in determining the degree of right to left shunt flow.[2] One of the consistent haemodynamic changes observed with laparoscopy is an increase in systemic vascular resistance,[3 4] which is helpful in this group of patients. While maintenance of systemic vascular resistance is very important, one must also avoid rises in pulmonary vascular resistance, which will increase right to left shunt flow and worsen systemic hypoxia. Hypoventilation from sedative premedication or postoperative analgesia, rising arterial carbon dioxide from absorbed gas at laparoscopy, and increased pulmonary airway pressure as intra-abdominal pressure increases, all contribute to increases in pulmonary vascular resistance.

We recently had a 39-yr-old man with complex congenital heart disease and Eisenmenger's syndrome present for laparoscopic cholecystectomy. This patient had uncorrected tetralogy of Fallot with a right-sided aortic arch, a large patent ductus arteriosus and right to left shunting via the duct. He had problems with recurrent ventricular tachycardia which was treated with amiodarone; polycythaemia requiring regular venesection; previous bacterial endocarditis; and ischaemic heart disease, evidenced by angina following venesection on several occasions. Other medical problems included hypothyroidism and chronic schizophrenia with mild mental retardation. He became dyspnoeic on even mild exertion and had seven episodes of cholecystitis in the four weeks before admission for cholecystectomy. On examination he was centrally cyanosed with marked clubbing and splinter haemorrhages. His pulse rate was 60 min^{-1} and regular, arterial pressure 120/60. His jugular venous pressure was not elevated, he had pronounced right ventricular heave and a holosystolic murmur with a loud second heart sound. Most recent echocardiography revealed a mildly dilated left ventricle with moderate decrease in function; an overriding aorta (50% left ventricle and 50% right ventricle) with a 2 cm ventricular septal defect and bidirectional shunting; a large right-sided patent ductus arteriosus with predominate right to left shunting; right ventricular hypertrophy; and a moderately dilated right heart with estimated right ventricular systolic pressures of 50 mm Hg.

During general anaesthesia for his laparoscopic cholecystectomy the intra-abdominal pressure was restricted to less than 15 mm Hg: the patient's systemic arterial pressure and oxygenation improved during the period of pneumoperitoneum without pharmacological intervention. During emergence from anaesthesia, the patient developed worsening hypoxia without changes in arterial pressure, heart rate or ventilation parameters. A visible increase in right ventricular heave developed, presumably reflecting increased pulmonary vascular resistance. Systemic oxygenation improved spontaneously over time as the depth of anaesthesia lightened and the trachea was extubated.

The same patient had a subsequent and unrelated admission for retinal detachment repair and during emergence from that anaesthetic, the same systemic hypoxia and pronounced right ventricular heave developed despite deep extubation and adequate spontaneous ventilation via a laryngeal mask airway. Again, oxygen saturation slowly improved as the patient awoke.

Changes in pulmonary vascular resistance need at least equal consideration as those of systemic vascular resistance in patients with Eisenmenger's syndrome. A selective pulmonary vasodilator such as nitric oxide or inhaled prostacyclin may be a useful adjunct to the management of such cases especially in circumstances where systemic vascular resistance is already very high.

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1. Sammut MS, Paes ML. Anaesthesia for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome. *British Journal of Anaesthesia* 1997; **79**: 810–812.
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Editor,—I read the article by Sammut and Paes[1] with interest and agree that the theoretical risks of anaesthesia in patients with Eisenmenger's syndrome (ES) are many and serious. I have anaesthetized a patient with ES for intracranial surgery.[2] The absence of obvious cyanosis and clubbing in the case reported is surprising. It is clear that maintenance of systemic vascular resistance is a necessary goal. It is worth mentioning that "fixed" pulmonary vascular resistance (PVR) preludes rapid adaptation to intraoperative haemodynamic changes and is usually unresponsive to pharmacological measures. The factors influencing PVR are important to know.

I remain unconvinced about "prophylactic" use of a norepinephrine infusion, which is continued into the postoperative period. The authors stated that there appeared to be a direct correlation between systemic pressure and oxygen saturation. But the higher systemic venous oxygen saturation and decreased oxygen consumption with induction of anaesthesia and muscle paralysis contributes to maintenance of arterial oxygen saturation during the intraoperative period in patients with cyanotic congenital heart disease (CCHD).[3] The authors did not mention any arterial blood-gas analysis. Peri-operative arterial blood-gas analysis is essential in a patient with ES undergoing laparoscopic cholecystectomy. The increase in end-tidal carbon dioxide after pneumoperitoneum under-estimates Pa_{CO_2} in patients with CCHD. Cardiorespiratory changes during laparoscopic cholecystectomy also increase the difference between end-tidal carbon dioxide and Pa_{CO_2}.[4] Monitoring for gas embolism in the presence of right to left shunt during laparoscopic surgery is necessary.

I believe conventional open cholecystectomy is advisable in the presence of ES. Mechanical effects of pneumoperitoneum (decreased cardiac index, impaired venous return, decreased FRC, increased V/Q mismatch and pleural pressure), hypercarbia and acidosis, the possibility of gaseous embolism and thrombotic complications are major side effects of laparoscopic cholecystectomy. These risks outweigh the benefits in a patient with ES. Slow persistent blood loss from the raw gall bladder bed as a cause of a nearly 50% decrease of haemoglobin concentration is difficult to understand. Were there any coagulation abnormalities?

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1. Sammut AS, Paes ML. Anaesthesia for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome. *British Journal of Anaesthesia* 1997; **79**: 810–812.
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Editor,—We thank Drs Kruger and Moran and Dr Patel for their interest in our article. Eisenmenger's syndrome is the end-stage in a disease process initiated by an anatomical communication between the pulmonary and systemic circulations. The blood flow across this shunt is initially from the high pressure systemic circuit to the low pressure pulmonary circuit resulting in increased pulmonary flow. If left uncorrected, this eventually culminates in irreversible pulmonary hypertension equal to and later, higher than, systemic pressure. The flow across the shunt is then reversed and a fraction of the deoxygenated blood returning to the heart enters the systemic circulation directly, bypassing the lungs and causing a drop in the arterial oxygen saturation. The flow of deoxygenated blood across the shunt is determined by the systemic pressure.[1, 2] A decrease in systemic vascular resistance (SVR) is accompanied by a decrease in pulmonary blood flow increasing hypoxaemia which in turn increases pulmonary vascular resistance further. Safety of anaesthesia in these patients is therefore dependent on maintenance of the SVR.

We agree that the SVR increases during laparoscopic surgery but this may be preceded by a decrease during induction of anaesthesia and the early intraoperative phase. As described in our article,[3] a short-acting vasoconstrictor delivered by infusion, such as norepinephrine, is particularly useful during this time and can be titrated very effectively as surgery proceeds. The rate can be increased if necessary towards the end of surgery when abdominal decompression and lack of surgical stimulation may allow the SVR to fall. The direct correlation that we noticed between the systemic arterial pressure and the oxygen saturation occurred intraoperatively and was therefore independent of the decrease in oxygen consumption associated with anaesthesia and muscle paralysis.

We agree that, because of the reasons mentioned by Dr Patel, the end-tidal carbon dioxide concentration (ET_{CO_2}) is a poor indicator of the absolute arterial carbon dioxide concentration (Pa_{CO_2}). It is nevertheless an appropriate indicator of trend and, in our view, adequate, given the very small observed change in its value and the short duration of surgery.

We share Dr Patel's concerns regarding the possible adverse effects and complications associated with laparoscopic surgery in patients in Eisenmenger's syndrome. Unfortunately, a decrease in functional residual capacity and cardiac index, an increase in pulmonary pressures and ventilation/perfusion mismatch are also seen with open surgery albeit to a lesser extent. Open surgery is associated with an increase in postoperative problems such as prolonged immobility, the generous use of opioid analgesia, decreased respiratory function and risks of deep vein thrombosis. We maintain that on balance, in the hands of experienced surgical staff, laparoscopic cholecystectomy compared with an open procedure has very few anaesthetic-related contraindications. The risks of gas embolism (especially important in patients with right to left cardiac shunts) are also considerably reduced by limiting the peritoneal pressure to 15 mm Hg and maintaining an anti-Trendelenburg position.

In their letter, Drs Kruger and Moran suggest that pharmacological manipulation of the pulmonary circulation would be of value in these patients. Unfortunately, i.v. pulmonary vasodilators are contraindicated as more often than not they dilate the systemic vasculature as well[4 5] and would clearly worsen the situation. Although both inhaled nitric oxide[6] and prostacyclin[7] have been shown to selectively reduce pulmonary vascular resistance in responsive patients, their role, in the conduct of anaesthesia for non-cardiac surgery in patients with Eisenmenger's syndrome, remains uncertain and cannot be recommended as agents of first choice.

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Extradural catheterization

Editor,—We read with interest the recent article by Bengtsson and colleagues.[1] Their report illustrates some important issues with regard to indications for extradural catheterization as well as problems with the practical management of such catheters. We have recently had a similar case. A 53-year-old man with severe cardiomyopathy was badly hurt in a traffic accident, suffering multiple fractures and contusions of the lungs and liver, and subsequently respiratory and renal failure. During surgery, a tracheostomy was inserted and he was treated in the ICU with artificial ventilation and haemodialysis.

Twenty-seven days after the accident, an untunnelled thoracic extradural catheter was inserted. A continuous infusion of bupivacaine and morphine was given through the catheter to treat thoracic pain, improve mobilization and facilitate weaning from the ventilator. Sixteen days after insertion of the catheter, there were signs of infection around the catheter at the skin exit site and the catheter was removed. Three days later the patient exhibited a paraparesis in the lower extremities with decreased sensibility to pinprick at Th12 and distally. Magnetic resonance imaging showed a large accumulation of fluid from Th3 to Th7. A laminectomy was performed immediately, and an extradural abscess drained. Methicillin was given. A culture subsequently showed growth of *Staphylococcus aureus* sensitive to methicillin. One month after the laminectomy the paresis had regressed and normal sensation had returned.

The strain of *Staph. aureus* cultured from the abscess was also found on the tip of the extradural catheter, in secretions from the tracheostomy cannula and in blood cultures taken during a febrile episode 5 days before extradural catheterization. The bacteraemia was treated for 5 days with methicillin.

This case illustrates the potential risk of serious nosocomial infection when an extradural catheter is inserted in a patient with known multiple colonizations of pathogenic bacteria, as is often the case in an ICU patient. It is at least in part related to the reduced immunocompetence that follows major trauma. This case also raises a question about the optimal management of extradural catheters under these circumstances. Is there, for example, any benefit from tunnelling such catheters, as seems to be the case with central venous catheters? A retrospective study with a rather small sample size does not favour this regimen.[2] The present case has also made us question the prevalence figures for serious spinal-space infections after extradural catheterization. Is it really as low as < 1:50 000?[3] Kvalsvik and Gisvold,[4] during 1 year, had two severely traumatized patients who developed extradural abscesses during extradural catheterizations of 11–14 days' duration. This would imply that the number of unrecorded cases may be substantial.

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Editor,—We think that the case described by Andersen and Sörensen well emphasizes the importance of a thorough consideration of the potential benefits and risks of a central neuraxial regional anaesthetic procedure in the potentially or overtly infected patient. Further aspects of the controversies about regional anaesthesia in the potentially infected patient are highlighted in the American Society of Regional Anaesthesia (ASRA) newsletter, February 1998, pp 4–6. A recent article in the official journal of the Swedish Medical Association[1] underlines the necessity of meticulous hygiene when performing spinal/extradural catheterization, with special emphasis on the mandatory use of good-quality face masks to avoid iatrogenic meningitis. This article also focuses upon the difficulties of reaching the correct diagnosis in certain patients with spinal-space infections. This supports the suspicion of Andersen and Sörensen that the prevalence of these infections is underestimated. The type of dressing (water-impermeable or not) used by the anaesthetist to achieve good fixation of the extradural catheter might also be important.

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1. Moen V. Iatrogenic post spinal meningitis, a rare sequela preventable by meticulous hygiene and face masks. *Läkartidningen* 1998; **95**: 628–635.

Use of laryngeal mask during tonsillectomy

Editor,—The laryngeal mask is becoming widely used for airway maintenance during tonsillectomy. The following case report documents a complication of such use which is potentially serious.

A healthy 17-yr-old male was scheduled for tonsillectomy. Anaesthesia was induced with propofol 200 mg and fentanyl 100 µg and the airway was maintained using a size 4 flexible laryngeal mask airway for spontaneous ventilation. After insertion of a Boyle-Davis gag, the airway was assessed with reference to the capnograph and chest movement, and found to be unobstructed. Coincident with removal of the first tonsil however, the airway became totally obstructed, as indicated by cessation of carbon dioxide emission, a tracheal tug with paradoxical respiration and development of arterial hypoxaemia. A quick assessment of the placement of the laryngeal mask revealed that the pilot tubing had become entrapped and severed by the snare used to remove the tonsil, and the cuff of the laryngeal mask had therefore totally deflated. In the face of brisk bleeding from the tonsillar bed, the mask was withdrawn following suction and a new mask inserted. This passed easily and the airway was re-established. At the end of surgery, the mask was withdrawn and direct laryngoscopy revealed only minimal soiling of the larynx and trachea with blood. Subsequent recovery from anaesthesia was uneventful.

Recent studies have suggested that the laryngeal mask airway has advantages over formal tracheal intubation for maintenance of the airway during adenotonsillectomy, with good surgical access and no increase in the incidence of aspiration of blood into the trachea.[1] Included in the complications recorded are laryngeal spasm after placement of the mask; obstruction of the airway after insertion of the Boyle-Davis gag, which has a reported incidence in the region of 20%[2 3]; and occasional airway problems during recovery and removal of the mask.[4] However, there does not seem to be a report of an airway complication during surgery resulting from inadvertent cutting of the pilot tubing by the surgeon.

The reason that this complication is more likely with the laryngeal mask is that, whereas the insertion of the pilot tubing into a 9 mm RAE profile tracheal tube (Malinkrodt) is approximately 4 cm behind the top incisors, the insertion of the pilot tubing of all laryngeal masks is into the cuff itself. This increases its predisposition to loop behind the tonsil where it is hidden from view during surgery. It is now my practice to tape the pilot balloon to the main tubing well proximal to its point of insertion, and not only to assess respiration but also to visually inspect the airway intra-orally after insertion of the Boyle-Davis gag.

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Method for reinserting the connector after cutting paediatric tubes

Editor,—The letter by Preis and Preis[1] has suggested a practical solution to the potentially fatal problem of damage to the connector while inserting it into the cut end of a paediatric tracheal tube. We would like to report the method we practise to avoid damage to the connector or the tracheal tube itself.

The tracheal tube is cut so as to make a short bevel. The connector is introduced at an angle to the tube, that is, directly facing the bevel (fig. 1). The bevel provides a wider area for initial insertion of the connector. Lubrication by a dab of soluble jelly at the tip of the connector facilitates its insertion. The connector is now brought into the longitudinal axis of the tube while maintaining a firm pressure when it gently slides into the tube (fig. 2). The last manoeuvre facilitates the insertion of the connector without damaging either the tracheal tube or the connector. As a result the connector can be inserted further into the tube. Visual inspection down the long axis of the tube detects any damage to the tube or the connector.

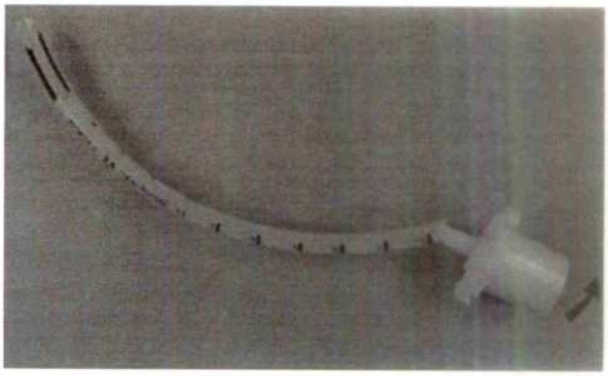

Figure 1 The connector is introduced facing the bevel made in the tracheal tube.

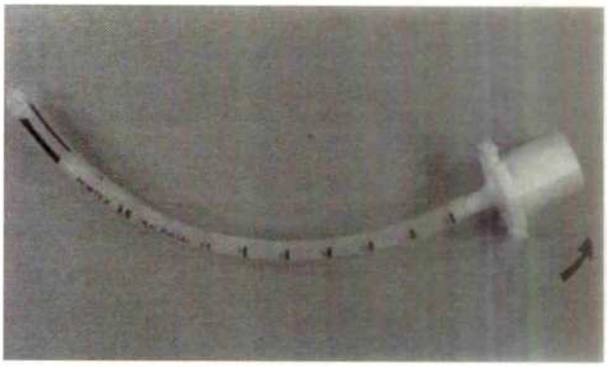

Figure 2 The connector is brought along the long axis of the tube.

This method eliminates the need for using a special paediatric airway adaptor or any dilatational instrument for he purpose.

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1. Preis CA, Preis IS. Obstruction of the lumen of a plastic 15 mm connector inserted into a cut paediatric tube—Is it possible to avoid this damage? *British Journal of Anaesthesia* 1997; **79**: 692.

Editor,—We agree in principle with the suggestion of Drs Dubey and Singh that cutting the end of a paediatric tube to make a short bevel helps to ease insertion of the connector. We would only caution that the angle of the bevel is of considerable importance to the air-tightness and the security of the join, as shown in figure 1, which clearly illustrates that the larger the angle the

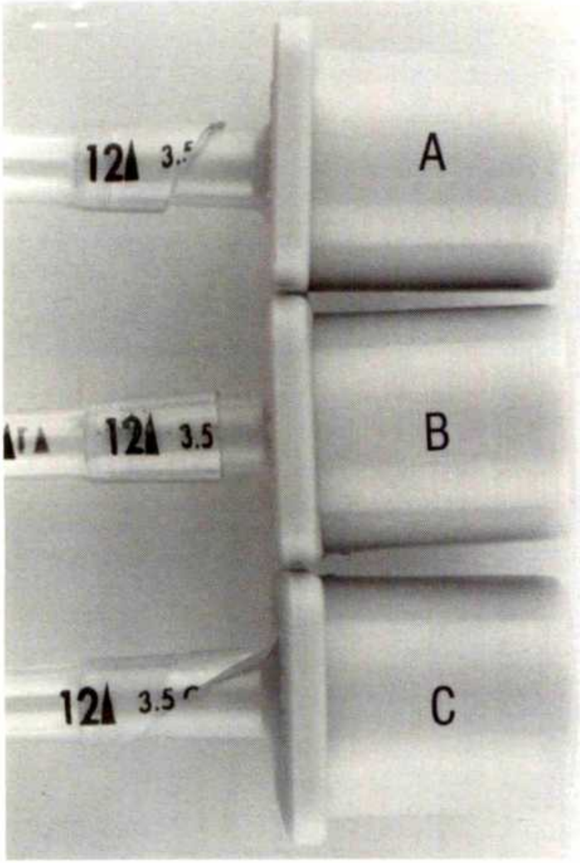

Figure 1 Connectors inserted into 3.5 mm internal diameter paediatric tubes cut at: (A) an angle of about 45°, (B) straight across, (C) an angle of about 60°.

more insertion length is lost. The key issue, of course, is that the connector be inserted far enough into the tube so that the connector/tube bond, which is guaranteed by our technique,[1] is not compromised.

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1. Preis CA, Preis IS. Obstruction of the lumen of a plastic 15 mm connector inserted into a cut paediatric tube—Is it possible to avoid this damage? *British Journal of Anaesthesia* 1997; **79**: 692.

British Journal of Anaesthesia 1998; **81**: 301–303

BOOK REVIEWS

Clinical Pediatric Anesthesia. J. M. Badgwell (editor). Published by Lippincott-Raven, Philadelphia. Pp. 512; illustrated. Price $85.00.

There are numerous American paediatric anaesthetists and about half of them appear to be busy writing textbooks. This is now a highly competitive business with many excellent, well-established books aiming for the same, relatively small, market. It is unsurprising, therefore, that the preface to this multi-author book tries to explain why we need another text on paediatric anaesthesia. The editor states that this book is aimed at everyone interested in the subject—the trainee, the generalist anaesthetizing the occasional child and the specialist—though I suspect this is more a marketing ploy than a realistic aim. The authors vary from the very well known to the completely obscure, but all are North American. In its typical American style the authors aim to inform us as to how they, "the experts", actually "do it". It does not pretend to be a comprehensive reference text, but a practical guide for the most commonly encountered paediatric anaesthetic problems. Although the size of the book means that some selection of material is inevitable, the text is usually pertinent, succinct and well written, though the style varied quite considerably. Editorial rewriting has been conspicuous by its absence and individual authors have, on the whole, been free to be as dogmatic, discursive or informal as they wish. The number of references per chapter varied from 15 to 162, though many were more than 15 years old.

The authors have succeeded in making this different from the average textbook, but whether you think this is necessarily a good thing will depend, I suspect, on your paediatric anaesthetic experience. The editor, J. Michael Badgwell, who works in Las Vegas, has gambled on the liberal use of cartoons and quotable quotes to keep the reader interested. I enjoyed reading many of the quotes, which although not always particularly relevant, were usually witty and perceptive. In contrast, I thought the cartoons were relatively unsuccessful, though they served to break up the text and made for an agreeable browse. The main problems with this book were its poor quality photographic reproductions and its "Americanisms". The descriptions of obsolete ventilators, use of intramuscular premedication, pentobarbital and "splash blocks" tended to grate. This book will appeal more to trainees than to experienced anaesthetists and cannot be recommended for departmental libraries. However, if you are a trainee interested in paediatric anaesthesia, then it deserves to be on your short list.

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Clinical Anesthesia Procedures of the Massachusetts General Hospital, 5th edn. W. E. Hurford, M. T. Bailin, J. K. Davison, K. L. Haspel and C. Rosow (editors). Published by Lippincott-Raven. Price £34.95 (International $40.00).

This is the fifth edition of a handbook which has become familiar to anaesthetists since the publication of the first edition 20 years ago; this reviewer acquired the second edition in 1983, and used it for several years. It is the work of many individuals at one institution who have attempted to produce a concise and didactic guide to practice.

The book is organized in three sections. The first section of seven chapters covers the implications of pre-existing medical illness. The next section of 28 chapters deals with the administration of the anaesthetic; almost half of these chapters concentrate on anaesthesia for a particular type of surgery. The other chapters deal with selected topics such as monitoring and transfusion therapy. There are three chapters on regional anaesthesia. A short third section has two chapters dealing respectively with resuscitation and with pain. There is an Appendix of over 40 pages dealing with commonly used drugs.

Each chapter is organized into a hierarchy of sections and subsections. These are denoted by Roman numerals, capital letters, Arabic numbers, and lower case letters. It is important to master this system, to navigate the cross references. One finds on page 253, for example "The mechanism ... is described in section IV.B.4.a"; one turns back four pages to find the start of section IV, and forward one page to find subsection B.4. The reader is helped by indentation of sections, and the use of bold type. While it is a matter of taste, this reader found the pages appeared more crowded than in the earlier edition, which had allowed a little more space between paragraphs. A book such as this depends heavily on the quality of the index, this comprises 71 pages, and is comprehensive.

Although it has over 800 pages, this book is small enough to be convenient to carry around. It measures 202 mm by 110 mm, and fits comfortably in the white coat pocket. Its thickness, 25 mm, is only slightly greater than that of the second edition. There are relatively few illustrations, though the chapter on regional anaesthesia has a fair selection of drawings.

The book emphasizes the common and important over the rare It is reassuring that the chapter on endocrine disease, for example, begins with five pages on diabetes mellitus, followed by three pages on thyroid disease. Rarer conditions are given less space. The book therefore is not a substitute for a reference work on the unexpected patient with an unusual condition. There are a few surprising omissions; rheumatoid arthritis is mentioned only in passing in the chapter on airway evaluation, and there is no chapter on non-traumatic orthopaedic surgery

This is not intended to be a book for the library; larger textbooks and specialist monographs can easily beat it for depth of coverage. But the anaesthetist who finds a few unplanned moments to spare will benefit from having this book at hand.

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Textbook of Intravenous Anesthesia. P. F. White (editor). Published by Williams and Wilkins, Baltimore. Pp 617; indexed; illustrated. Price £80.00.

I.v. anaesthesia has been growing in popularity in recent years, especially with the introduction of target controlled infusion systems; a comprehensive text on the subject is therefore timely. Although the contributors are predominantly North American, there are important contributions from European authors as well.

The whole text is divided into various sections. An Introductory section (perhaps better called Basic Principles) is followed by two large sections on the pharmacology of hypnotics, and analgesics, and a relatively smaller section on neuromuscular blocking agents. The section of Basic Intravenous anaesthetic techniques is a mixture of techniques and the use of other drugs in i.v. anaesthesia. There are useful chapters on drug delivery systems, monitoring the depth of anaesthesia and the use of i.v. anaesthesia in different patient populations and the future of i.v. anaesthesia The sections on hypnotics and analgesics are detailed and rightly form the core of the book and lay the foundation of the practice of i.v. anaesthesia. Some of the drugs described that are not used now could have been described in a historical section.

There are some inconsistencies in the book. For example, there are separate chapters entitled "Balanced Anesthesia" and "Total Intravenous Anesthesia". Is the latter not supposed to be balanced? It is also noticeable that pharmacokinetics are described in many of the chapters apart from the ones in sections I–IV. Why are neuromuscular blocking agents described in a separate section when, like many other agents, they are truly adjuvants? I would have thought that at least their use by infusion would have been described in some greater detail! It would have been useful to describe management of postoperative analgesia, particularly in view of the use of shorter-acting agents for maintenance; the use of local anaesthetics and NSAIDs could have been described in a better perspective. As such, some of these chapters appear no different from those found in standard pharmacology texts The major development in the use of "Target Controlled Devices" came after the book had been written.

Notwithstanding the above criticisms, *Intravenous Anesthesia* is a useful book Almost all the chapters are comprehensively referenced although it is difficult to find many after the year 1994. It is written clearly and well produced. The illustrations are clear and help in the understanding of the text. The enthusiast may well buy it but at its price, it is a book for departments and libraries. A particular pleasure for me was to notice that Dr White has dedicated this book to the memory of Professor John Dundee, a pioneer of i.v. anaesthesia well known on both sides of the Atlantic ocean.

R. K. Mirakhur

The Genesis of Surgical Anesthesia. W. A. Bergman. Published by Wood Library, Museum of Anaesthesiology, Illinois. Pp. 448; indexed; illustrated. Price $85.00 (postage $35.00).

If a question is asked about the identity of the "discoverer" of anaesthesia, the answer given might be Morton (Boston, 1846), although claims could be entered for Simpson, Wells, Hickman, Davy, and perhaps others. In the preface to this book, the author suggests that the question is futile, as many pathways led to Morton's demonstration, and a critical factor in his success was the speed with which others spread the news and disseminated it widely

Professor Bergman takes the events of the early decades of the 19th century as the end-point of a "stepwise and incremental" development over many hundreds of years and draws on a wide range of sources. There are chapters on the Medicine of the Ancients, Developments up to the 16th century, and Pneumatic Medicine, as well as individual chapters on Priestley, Lavoisier, Beddoes, and Davy, and concluding sections on the use of nitrous oxide and ether, and anaesthetic techniques before 1846.

The outcome of this approach is that, including those on the life and works of Beddoes and Davy, eight of the 18 chapters are related to the subject of Pneumatic Medicine, and the longest chapter in the book (36 pages) is devoted to the Lunar Society of Birmingham and its influence on anaesthesia. There is a significant volume of literature in this area already, but the author contends that there is still a good deal that has been neglected. The scope and balance of these chapters may cause some surprise, but Professor Bergman anticipates criticism and points out that general anaesthesia, together with oxygen and other forms of inhalation therapy, are, after all, examples of pneumatic medicine in practice.

Besides the names mentioned above, there are also "synoptical" biographies of individuals with an interest in scientific investigation, particularly related to the properties of gases and to respiratory and circulatory physiology. Again the relevance of some of these may be questioned but as a historian, Professor Bergman believes that they are intrinsically interesting and worthy of attention. He makes no claim that a knowledge of history is essential to become a competent clinical practitioner, but recommends it for its ability to add variety and interest to a working life.

There is certainly a wealth of enjoyable personal detail. We are familiar with difficulties in the lives of Jackson, Morton and Wells, but some of their predecessors cannot have been easy to live with. Paracelsus was "difficult" and addicted to drink, Priestley was a dissenting minister and supporter of the French Revolution, and Beddoes was on a Home Office list of "disaffected and seditious persons". Davy and Coleridge had a long standing friendship; Coleridge was interested in Davy's researches into nitrous oxide (perhaps not surprising in view of Coleridge's experience with opium), and Davy attempted to write some verses. Samuel Johnson wrote a biography of the Dutch chemist and physician Boerhaave, and according to Boswell, was fond of performing chemical experiments. Clearly, the question of the two cultures was not a debating point. There is a noteworthy coincidence that Beddoes was born in the small Shropshire town of Shifnal, where Hickman later practised.

The book is attractively bound and printed, with a black and white plate at the beginning of each chapter, though it should be mentioned that the base of the spine on the review copy developed a tear after not particularly robust use. There is a superb collection of references (over 800) but they are not conveniently arranged. A number in the text refers to a name and date under chapter headings at the end of the book; the full references are listed alphabetically a few pages further back. The author concedes that the sources are almost exclusively in the English language.

There is low incidence of misprints and inaccuracies, although for some reason chapter xv (on the Lunar Society) is less exemplary in this respect. Lichfield is persistently misspelt as Litchfield, and is described as a town, which may disappoint the residents and the Dean and Chapter of the cathedral. Few people will have heard of a diarist called Pepyps (footnote, p. 297). There is a bit of overlap and repetition, but given the relationships between the Pneumatic Institute, the Lunar Society, and the Royal Society, this is probably inevitable and in the long run helpful.

The above complaints are trivial and should not discourage anyone from reading this book. I suggest that it is a must for libraries and institutions. The expanding membership of History Societies on both sides of the Atlantic suggests an increasing interest in this area and for these the book will be of great interest. The author hopes that it will also appeal to interested laymen, as an effort is made to explain chemical formulae and medical terms. The literary style is easy and polished. It is a considerable achievement.

P. M. E. Drury

Measurement of Pain in Infants and Children. Progress in Pain Research and Management, vol. 10. G. Allen Finley and Patrick J. McGrath (editors). Published by International Association for the Study of Pain, IASP Press, Seattle. Pp. 210; indexed; illustrated. Price $67 00.

The editors have assembled a dazzling array of contributors from Canada, the United States of America, the United Kingdom and Australia to produce a classic summary of the techniques available for the measurement of paediatric pain in 1998. They place this book firmly in context in their introductory chapter where they state "We hope that this book will provide a starting point for health professionals and researchers to develop and use reliable, robust, and practical techniques for measuring pain in children, which will result in improved care and, eventually, in the universal acceptance that pain prevention and treatment are of the highest priority in the care of children." This aim is achieved admirably with detailed consideration of the basic principles of measurement techniques, the neurophysiological basis of measurement technologies and the physiological and behavioural measures of pain. Colour photographs enhance a brilliantly clear description of the facial display of pain by Kenneth Craig. Self-reporting of pain experience by children is discussed in detail. This is a most expert, balanced critique with the available self-report measures checked against the elusive "ideal". Assessment of the emotional component of pain is discussed in this chapter and this resonates with the IASP's definition of pain "an unpleasant sensory and emotional experience. ." This is developed further in the next chapter where composite measures of pain are beautifully summarized. The use of these multidimensional assessment tools is becoming more widespread in groups of children where self-reporting is not possible. this section points out their advantages and limitations The final chapter draws the threads together in illustrating how the thorny issue of incorporating the available paediatric pain measurement techniques into routine clinical practice can be tackled. On the one hand this is an interesting description of how change has been managed in a number of institutions. But on the other, this chapter illustrates the very problem the authors are trying to solve, the one of making the whole process excessively complex and obscured by scientific detail. The pragmatic approach adopted by many acute pain management services is hinted at but surely warrants inclusion because it is so successful. A series of cycles of simple assessments repeated frequently, which are acted upon using simple protocols and a limited pharmacopoeia, allied to non-drug measures to minimize pain and adverse effects, has been shown to work well in paediatrics. This assessment-intervention-reassessment approach allows individualization of pain management and can also be applied to the control of long-term pain. The routine measurement of pain is very important but the danger of "routinization" is that the measurements are not acted upon. This reviewer will be using this book to design better ways of linking individualized pain prevention and control to individualized pain assessment. You can do it too, because this excellent book contains all the information you need to learn how to measure pain in infants and children. You can find the information readily via the comprehensive index and reference lists and if you find any gaps, you are given an address, telephone number, fax number and e-mail contact for each chapter! There really is no excuse for not proselytizing in your institution!

N. S. Morton

Advanced Cardiac Life Support. The Practical Approach, 2nd edn. P. Driscoll, C. Gwinett, K. Mackway-Jones and T Wardle (editors). Published by Chapman and Hall Medical, London. Pp. 260; indexed, illustrated. Price £24 99.

In 1990, a group of affiliated health care professionals drawn from five clinical specialties formed the Advanced Life Support Group; their aim was to improve the standards of acute medical care following a cardiac arrest. This development followed the establishment of the United Kingdom's first Advanced Cardiac Life Support (ACLS) course at St Bartholomews' Hospital in 1987. The first edition of this book, published in 1993, was designed primarily as a course manual for students participating in ACLS provider courses. It aimed to provide a concise guide to the management of cardiac arrest beginning with basic life support, and continuing right through to post-resuscitation care and bereavement counselling. The second edition of the book has the same principal aim but is no longer a course manual. This follows the introduction in 1995 of a unified Advanced Life Support course (with separate student manual) resulting from the amalgamation of courses run by the ALS group and the Resuscitation Council (UK).

This edition covers much of the same material as the first and attempts to provide healthcare workers with an understanding of the principles of managing a cardiac arrest, including a guide to the practical procedures involved. The book is divided into four main sections with two appendices and a comprehensive index. The text is well illustrated with line drawings, flow diagrams and ECG rhythm strips. The first introductory section consists of four chapters covering a brief general introduction to the cardiac arrest situation, the natural history of myocardial infarction, pharmacology of the relevant drugs, and a chapter on acid-base balance and blood-gas analysis which has been extensively revised. Although this book does not claim to be comprehensive, the chapter covering pharmacology is particularly sketchy.

The second section on life support is divided into seven chapters covering basic and advanced life support, including management of the airway, access to the circulation, arrythmia recognition and treatment, and post-resuscitation care. New guidelines for basic life support issued by the resuscitation council in 1997 are presented. A simplified algorithm for the management of adult cardiac arrest based upon statements by the International Liaison Committee on Resuscitation is also included. The chapter on post-resuscitation care is no more than a brief introduction to some aspects of intensive care management of the post-cardiac arrest patient.

Section three, entitled "Special Situations", consists of two chapters, the first of which covers paediatric life support. The principles of basic paediatric life support are well explained and will be of use to those who have no paediatric experience or have not undertaken a paediatric life support course. Although treatment regimens for advanced life support are also included, post-resuscitation care is dealt with only briefly. The second chapter contains useful guidelines for the management of cardiac arrest in special circumstances such as near drowning and electrocution, and has been revised and updated to include volatile substance abuse and anaphylaxis.

The fourth section is devoted to the practical procedures involved in managing a cardiac arrest including securing the airway, gaining access to the circulation and performing needle thoracocentesis, chest-drain insertion and pericardiocentesis. It is noteworthy that the second edition is not a course manual and that there can be no substitute for practical tuition as a means to acquiring these practical skills. Finally, there are two appendices that deal with failed resuscitation and ethical and legal considerations.

This book attempts to cover a large amount of material and is of necessity brief in places. However, the principles of basic and advanced adult life support are well presented, and this book will undoubtedly appeal to those involved in ACLS courses and resuscitation training.

K. Mills

Methods in Molecular Biology, vol 100: Nitric Oxide Protocols M. A. Titheradge (editor). Published by Humana Press, New Jersey. Pp. 336. Price £55.00.

This book is the hundredth in the series *"Methods in Molecular Biology"* and the twelfth in the series to be published this year. It is multi-author; 57 experts from England, USA, Spain, Germany and Austria contribute 30 chapters. Although the book contains a lot of information on molecular biology techniques relating to nitric oxide, it also contains details of biochemical, chemical and mathematical techniques, making it more comprehensive than the series title would suggest.

The book begins with an introductory chapter on the enzymology of nitric oxide synthases. The remaining 29 chapters describe laboratory protocols relating to nitric oxide, and are all in the same format of introduction, materials, methods, notes and references. The protocols are all detailed, and comprise lists that describe the protocols step-by-step. The notes give the common errors and pitfalls for each technique.

The protocols cover eight main areas. Protocols for purification of nitric oxide synthases, cloning nitric oxide synthases, measuring nitric oxide synthase mRNA, localization of nitric oxide synthases and measurement of nitric oxide synthase activity make up more than half of the book. Also covered are methods for indirect measurement of nitric oxide formation, using nitric oxide donors and measuring the toxic effects of nitric oxide.

This is obviously a reference book and laboratory manual for laboratory workers in the field who want details of the "nuts and bolts" of assays and techniques which are more briefly described in papers, rather than a text book. A basic knowledge of laboratory techniques is assumed. As with a cookbook, the best test is how the recipes turn out. I compared the instructions for three assays described in the book with our protocols for the same assays In each case, the descriptions were accurate and comprehensive, and the notes section described nearly all of the problems we had encountered.

This is not the only book published which brings together nitric oxide protocols. *"Methods in Nitric Oxide Research"* by Feelisch and Stamler (John Wiley and Sons 1996; ISBN 0-471-95524-8) is also a collection of descriptions of research methods, but the two books complement rather than compete with one another. Feelisch and Stamler's book deals far more with the chemistry and biochemistry of nitric oxide, and contains more background information and less of the fine detail of techniques. This book concentrates far more on the molecular biology of nitric oxide and very detailed descriptions of laboratory techniques.

This book is a must for laboratories with an interest in nitric oxide, but may not be widely read if brought for an anaesthetic library.

J. D. Young

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

Education and training in airway management

Airway management is the scaffolding upon which the whole practice of anaesthesia is built. Consequently, education in airway skills must occupy a central place in anaesthetic training, since it is within the realms of respiratory management that the penalties for misadventure are greatest. Adverse respiratory events accounted for more than one-third of 2046 US closed malpractice claims[1] and the commonest causes were inadequate ventilation, oesophageal intubation, difficult intubation and airway obstruction.[2] Eighty-five percent of these respiratory events resulted in brain damage or death, 72% were judged by the assessors to have been preventable and 75% involved substandard care.

As concurrent failure of tracheal intubation and mask ventilation may ultimately result in death or brain damage, these two basic techniques are the most important that an anaesthetist learns. Unfortunately, there are three factors that have combined to reduce trainees' exposure to tracheal intubation and mask ventilation in the past few years: reduction in time spent in the operating theatre; introduction of other means of managing the airway; and a greater use of regional anaesthetic techniques. In addition, there is a perception among UK trainees that the basic techniques are easy and not worthy of the meticulous, disciplined approach they deserve. This observation has sometimes been made by overseas visitors.[3]

Until recently, anaesthetic training was relatively unstructured, so that skills and knowledge were acquired haphazardly. However, this deficiency was partially minimized by the length and breadth of the apprenticeship. Recent condensation of specialist training in the UK[4] and the decreased time now spent in the operating theatre have made it imperative that anaesthetic training as a whole should become more organized. This applies particularly to airway management. Instead of learning the use of a simple face mask and tracheal tube, today's trainee is faced with an ever increasing number of airway devices and techniques. Not only must the trainee be taught how to use new equipment, but when and when not to use it. Airway safety may be compromised easily by performing a good technique badly, or by using it in inappropriate circumstances.

Even before publication of the Calman Report,[4] several departments had seen the importance of specific airway training, but efforts were concentrated mainly on providing short-term courses on special techniques for the difficult airway. Several have pioneered national workshops, while a few provide specific airway rotations within the conventional training schedule.[5 6] These are considered excellent by anaesthetists fortunate enough to attend, but are expensive, time consuming and relatively exclusive. There is also a danger that substantial investment in the provision of concentrated experience for the privileged few may result in dilution of training opportunities for the majority. Difficult techniques, however, cannot be mastered during short workshops, and skills need practice and repeated reinforcement.[6] Short, concentrated courses should be considered supplementary to in-house teaching. Expertise in airway management can only be acquired gradually, over a long period of clinical experience, not in a few days.

At present, relatively few hospitals attempt to coordinate the training of airway management. A recent survey of tutors of the Royal College of Anaesthetists noted that only 37% of UK departments offered formal airway training and few actually provided details of the modules.[7] Similar deficiencies in postgraduate programmes have been shown in the USA.[8]

How can teaching in airway management be improved? The Royal College of Anaesthetists provides an extensive syllabus of subjects for the FRCA examinations[9] and details of modules, training objectives and assessments.[10] Each specialty module contains some elements pertinent to the airway, but these are never specifically drawn together to provide a comprehensive airway syllabus.

There is little guidance for consultants as to how to teach modern airway management and little research undertaken into educational methods that are directly relevant to postgraduate training in anaesthesia. The present situation, in which consultants are required to organize a 24-h clinical service in anaesthesia and at the same time provide individualized teaching for groups of itinerant Calman trainees, must be unique. In what other profession would untrained teachers, with little time and fewer facilities, be expected to provide comprehensive education for trainees with such widely different levels of experience?

Emphasis has been placed on the future of electronic means of teaching. Some excellent videos have been made, but the full potential of interactive CD ROMs has still to be realized. Teleconferencing is not the answer for the medical postgraduate. Even in undergraduate education, experts in the field are agreed that electronic networks have yet to achieve their proper role[11] and it is unlikely that they can ever replace the experience of diagnosing and treating a patient.[12] Theatre-type simulators[13] can only play a minor role in airway training, as they are intended primarily to prepare the anaesthetist to manage a crisis. In teaching airway management, the emphasis should be on how to avoid the crisis situation. Airway training should be primarily for peacetime, not for war.

Unfortunately, there can be no substitute for working at the coal-face. Those who have forged the new postgraduate education strategy have failed to recognize the special needs of trainees in the artisan specialties of surgery and anaesthesia. Facts and theory can be learned from books and in the classroom. They can be reiterated when required for examination, lecture and interview purposes. Individual manual skills can be taught in isolation. However, it is only in the work place that the trainee can learn to combine these, together with the indefinable philosophies of judgment, experience, humanity and ethics, into the total process of "giving an anaesthetic".

The most important places for anaesthetic training are the ward, the operating theatre and the intensive care unit, not the classroom and the library. The influence of clinical teachers as role models for students cannot be underestimated.[14] Good anaesthesia teachers combine enthusiasm, willingness to teach and an "inquiry" approach.[15] The worth of such clinicians must be recognized formally and time and facilities made available, to avoid frustration and burnout.[16] Many hospital consultants involved in the emergency specialties of anaesthesia and surgery are now retiring early and the profession can ill afford this loss of experienced teachers.

These are the problems. What are the solutions? The initial steps require commitment, organization and money. The Royal College, members of the profession, and trainees must acknowledge that: modern airway management requires special attention; the majority of training must be done in the workplace, not in special centres; and it consumes resources. Funding will be required from Postgraduate Deans, NHS managers and purchasers, so that each anaesthetic department involved in training can equip an airway training room.

The contents of a syllabus of both basic and advanced airway management must be agreed. Airway management should be interpreted in its widest possible sense. It should encompass the theory and practice of a variety of respiratory-related procedures and associated equipment. It will include the basic skills of airway assessment, mask ventilation, tracheal intubation and airway decision making, in addition to the more advanced techniques of fibreoptic intubation and percutaneous tracheostomy. One or two consultants with the appropriate expertise should be identified as coordinator/s. However, every consultant has something to offer and the teaching load should be spread widely.

On arrival in a new department, each trainee, whatever grade, should be given the syllabus and the aims explained. The syllabus can be used by the trainee as a checklist and by the trainer as a prompt for teaching or inquiry during a theatre session. However, it should be made clear that the ultimate responsibility rests with the trainee to maximize the experience obtained during each relevant part of training. For example, during the ENT module, discussion of upper airway problems, endoscopies, laser techniques, special tubes, Venturi systems, etc., would take place.

The coordinator should document the initial encounter, the trainee's particular requirements and attendance at group training sessions. A register will help to emphasize the more formal nature of the new arrangements and allow the coordinator to assess a trainee's progress from time to time. An intended function of the log book was to enable trainees to identify their own deficiencies. Strang showed that they were rarely used for this purpose.[17] Trainees require prompting, but recognition of their own responsibilities within the new system is fundamental. Unfortunately, the reduction in hours of work has fostered a minimalist approach by some trainees. However, procedures, problems and patients do not necessarily present at convenient times and it must be accepted that flexibility and initiative are essential components of professional training.

A training room must be equipped within the anaesthetic department. Airway management training is entirely different from resuscitation training and must be kept separate. However, as with CPR training, the use of manikins is now essential for several reasons. The patient must be protected from the total novice. Some of the new airway procedures are relatively complex, therefore the trainee must be given the opportunity to practise manoeuvres in an unstressful way. Disposable items are relatively expensive, but experience and use of the components can be economically gained by reusing them on a manikin. The quality of manikins improves steadily, as does their specific teaching value. Scopin II Bronchoboy (Adam, Rouilly Limited, Sittingbourne, Kent) is a dedicated bronchoscopic trainer with detachable lungs and bronchial tree. It can be used for manipulation of the fibreoptic bronchoscope through the larynx and the bronchial tree and for learning bronchoscopic anatomy, with and without the chest wall in place. A cricothyrotomy simulator (VBM Medizintechnik GmbH, Freelance Surgical Promotions, Bristol) can be used for practising cricoid pressure technique, cricothyrotomy, setting up a Venturi device and simulating retrograde intubation techniques. Audiovisual facilities should be available within the department and a library of videos and CD ROMs can be built up gradually. After the initial purchases, a modest maintenance budget is required to provide new items, replace worn ones and renew disposable parts.

The department should agree on a simple scheme for the management of the unexpected difficult intubation/airway. This could be based on the algorithm approved by the American Society of Anesthesiologists.[18] However, it is important that the complex-looking posters that adorn many anaesthetic room walls should be simplified into a number of logical steps. The basic manoeuvres that optimize initial attempts at intubation and mask ventilation must be emphasized.[19] After such a plan has been agreed, a trolley should be equipped to contain only those items specified in the algorithm. Each item on the trolley should be duplicated in the training room, so that trainees have the opportunity to practise their use on a manikin. Every new intake of trainees must attend a training session and regularly examine the trolley.

Before allowing a trainee to undertake an advanced technique such as fibreoptic intubation or percutaneous tracheostomy on a patient, considerable preparation should have taken place. Complex skills are best learned gradually, by dividing the complete process into several simpler tasks.[20] For fibreoptic intubation, there are numerous opportunities to learn outside the operating theatre. Attendance at diagnostic bronchoscopy lists[21] and ENT outpatients[22] allows trainees to obtain useful tips from other specialists, while practice on the manikin improves manual skills.[23] Fibreoptic techniques can be acquired by graduated training.[20] Only those trainees who have already demonstrated their mastery of the basic steps should be given the opportunity to perform the technique under supervision. Percutaneous tracheostomy presents similar teaching challenges and the report in this issue of the journal of a method of training, using an animal model and a video camera, demonstrates the ingenuity of some trainers in devising new ways of teaching more complex techniques.[24]

The length of time to complete specialist training has been reduced, but as yet there is no evidence that anaesthetists can acquire sufficiently wide clinical experience and education within this limited time scale.

One implication of the new Calman training system is a greater dependence on teaching by ordinary practising clinicians,[25] most of whom are untrained for this role. These major changes have been made with little or no provision for support at this level, no formally recognized time for teaching and no investment in modern teaching facilities.

While airway management is only a single aspect of anaesthetic training, it is probably the one for which the availability of good teachers and training equipment are most essential. Anaesthetic departments must have trainers with dedicated time in which to teach airway management and a budget with which to equip an airway training room. The cost of these initial steps would be small compared with the price of a single failure of airway management that resulted in brain damage or death. Resuscitation training is already well established within hospitals. There is even more reason to provide similar facilities for airway management training.

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EDITORIAL II

Adrenocortical function in critical illness

Most critically ill patients exhibit increased plasma cortisol concentrations.[1] However, the report of Duggan, Browne and Flynn published in this issue of the journal serves as a reminder that adrenocortical insufficiency exists as a potentially treatable component of critical illness.[2]

What constitutes normal adrenocortical function during critical illness remains unclear. Although there have been several reports on the subject, the conclusions are controversial.[3] What is incontrovertible is that adrenocortical function is essential for host survival during critical illness. Doses of endotoxin or live *Escherichia coli*, which are sub-lethal in normal animals, are lethal when administered to adrenalectomized animals.[4] In adrenalectomized primates receiving sub-physiological doses of corticosteroids, cholecystectomy produced marked cardiovascular instability compared with intact or adrenalectomized animals receiving supra-physiological doses of corticosteroids.[5] Hypotension in the former resulted from decreased cardiac index and peripheral vascular resistance. This is not surprising as corticosteroids are known to enhance myocardial contractility and vascular smooth muscle tone in response to adrenergic stimuli, mainly by increasing adrenoreceptor sensitivity to catecholamines.[6]

Investigators have measured plasma cortisol concentrations in different subgroups of critically ill patients. Those with bacterial infections,[7] septic shock,[2] and other acute medical[8 9] or surgical[10] conditions generally have increased plasma cortisol concentrations. Although the majority of studies report increased cortisol concentrations in critical illness, the range of measured concentrations is wide. They vary from those observed in healthy individuals to up to 20 times these values.[3] This scatter makes it difficult to define a normal range for plasma cortisol concentrations in critical illness.

Some studies have reported a significant correlation between plasma cortisol and adrenocorticotrophic hormone (ACTH) concentrations in critical illness.[11] This increase in pituitary secretion of ACTH may be at least partly responsible for increasing cortisol release from the adrenal gland. However, other studies have failed to demonstrate such a correlation, particularly in non-survivors, which suggests that in some patients the hypothalamic–pituitary–adrenal axis may be impaired during critical illness.[1] Hypercortisolaemia in critical illness may result not only from increased adrenocortical release but also from a decreased rate of cortisol extraction from blood,[12] lower cortisol binding globulin concentrations[13] and reduced hepatic extraction.[14]

The precise incidence of adrenocortical insufficiency in critical illness is unknown. Values ranging from 0% to 41% have been reported.[3 15] Sibbald and colleagues assessed adrenocortical responsiveness in patients with septic shock using an ACTH stimulation test and reported a subnormal cortisol response in 19%.[7] In a large series, Finlay and McKee found that 27% of critically ill patients had low plasma cortisol concentrations.[16] In another study, they reported that 12 critically ill patients with low basal cortisol concentrations also had abnormal responses to ACTH.[17] In a more recent study, 24% of patients with septic shock exhibited adrenocortical insufficiency after ACTH stimulation.[18]

In contrast, only 3% of *very sick* patients were reported to have low random plasma cortisol concentrations.[19] Moreover, another group found that only 2% of critically ill patients had abnormal responses to ACTH administration, and of these 50% had been receiving long-term corticosteroid medication.[20] A variety of reasons may explain the wide range of reported incidences of adrenocortical insufficiency. These include: method used to diagnose adrenocortical insufficiency (basal plasma cortisol concentrations, response to ACTH stimulation, or both); use of cortisol normal ranges derived from healthy individuals to detect adrenocortical insufficiency in the critically ill; and absence of standardization in the design of these studies, particularly in defining patient groups.

The question of how adrenocortical function in critical illness should be assessed remains unanswered. Absolute adrenocortical insufficiency, which results in very low plasma cortisol concentrations, which alone may be diagnostic, is unusual in the critically ill. It may result from massive bilateral adrenal haemorrhage as a complication of coagulopathy or severe thrombocytopenia,[21] adrenocortical suppression from long-term corticosteroid administration[20] or drugs such as etomidate or ketoconazole.[22] The diagnosis of relative adrenocortical insufficiency (supra-normal basal but deficient post-stimulation increase in plasma cortisol concentrations) is more controversial. Most investigators now regard an ACTH stress test as essential in the assessment of adrenocortical function. To date, most authors have introduced their own criteria for the diagnosis of adrenocortical insufficiency in critical illness. These are broadly similar to the values of basal and post-stimulation plasma cortisol concentrations used for the diagnosis of adrenocortical insufficiency in healthy individuals. Hypocortisolaemia appears to be common in septic shock.[23] It has also been suggested that low plasma cortisol concentrations do not necessarily indicate functional adrenocortical insufficiency and that adrenocortical insufficiency can only be detected with certainty after an ACTH stress test.[23] However, even if the values for increment and minimum peak plasma cortisol concentrations after ACTH stimulation observed in healthy individuals prove to be acceptable in making the diagnosis of adrenocortical insufficiency in the critically ill, there are still potential difficulties in interpreting the results. The absence of a post-stimulation peak in cortisol response in critically ill patients with high basal plasma cortisol concentrations would be difficult to explain.[3] Whether this represents a state of maximally stimulated, and therefore appropriately functioning adrenal cortex or relative adrenocortical insufficiency, is still a matter for debate.

Certain factors in the patient's medical history should lower the clinician's threshold for diagnosing adrenocortical insufficiency in critical illness. These include the presence of a bleeding disorder, chronic steroid administration and the use of other adrenocortical suppressing drugs. Other important factors include a history of tuberculosis, metastatic malignancy and autoimmune disease. Moreover, there are subtle and less appreciated causes for adrenocortical dysfunction in critical illness. Hypopituitarism, either in its chronic form unmasked by critical illness, or its acute variant resulting from pituitary infarction or trauma, may be an important contributory factor to adrenocortical insufficiency in some patients. It may be suggested by other indirect indicators of hypothalamic–pituitary dysfunction, such as abnormal thyroid function tests. Hypotension may produce adrenal ischaemia and could be a cause of adrenocortical insufficiency. Bilateral adrenocortical haemorrhagic necrosis has been reported in 30% of patients who die from septic shock.[24]

Previous observations suggest that circulating mediators in critically ill patients can reduce the ability of adrenocortical cells to respond to ACTH. *In vitro*, adrenocortical cells produce less cortisol in response to ACTH after incubation with plasma from rabbits with septic shock compared with cells incubated with control plasma.[25] The active component in that study may have been tumour necrosis factor-α (TNF-α) which has been shown to reduce the production of cortisol by human fetal adrenal cells.[26] However, under certain conditions this cytokine can paradoxically stimulate adrenocortical function.[27] A direct correlation between plasma TNF-α and cortisol concentrations was observed in patients with septic shock, but this relationship was not seen in septic shock complicated by adrenocortical insufficiency.[18]

Human lymphocyte-produced fragments of ACTH[28] and corticostatin,[29] an immune cell-derived peptide, can bind to ACTH receptors and thus decrease the response to endogenous ACTH. It is conceivable that high expressers of these molecules may be at risk of developing adrenocortical insufficiency during critical illness. It has been recognized recently that interleukin-6 (IL-6) can activate the pituitary–adrenal axis.[30] Both IL-6 and ACTH concentrations were lower in critically ill patients with adrenocortical insufficiency compared with those with adequately functioning adrenal glands.[18] These studies suggest that a deficient IL-6 response may contribute to adrenocortical insufficiency through understimulation of the pituitary–adrenal axis.

Some studies have suggested a relationship between plasma cortisol concentration and severity of illness.[31] However, there has been no convincing evidence that measured increases in cortisol concentrations in critical illness are useful in predicting patient outcome.[1] Many studies support the hypothesis that adrenocortical insufficiency in critical illness increases mortality.[7] Adrenocortical insufficiency almost doubled mortality at 4 weeks from 44% to 80% in patients with septic shock.[18] Furthermore, a subnormal response to ACTH in septic shock was associated with a significantly higher mortality.[15] Although hypocortisolaemia was not uncommon in patients with septic shock and did not itself predict increased mortality, adrenocortical hyporesponsiveness was predictive of poor outcome.[23] However, other studies have cast doubt on the belief that adrenocortical insufficiency is associated with increased mortality in critical illness. Schein and colleagues failed to find a relationship between low plasma cortisol concentrations and increased mortality.[5] Others also reported that neither baseline nor peak plasma cortisol concentrations after ACTH stimulation were useful in predicting mortality in critically ill patients.[1] In fact, higher plasma cortisol concentrations were found in non-survivors which suggests that high cortisol concentrations may be a marker of disease severity. This controversy has probably arisen because of the current imprecise definition and identification of adrenocortical insufficiency in critical illness. This can only be resolved when a reliable and reproducible method for the diagnosis of adrenocortical insufficiency in critical illness is established.

Two double-blind, placebo-controlled studies and a recent meta-analysis concluded that administration of corticosteroids produced no overall benefit in sepsis and septic shock.[32–34] As a result, the use of exogenous corticosteroids in critical illness has declined. It is likely that some critically ill patients who several years ago may have inadvertently received corticosteroid treatment for adrenocortical insufficiency may now not be treated. Although there is still uncertainty about the diagnosis of adrenocortical insufficiency and its relationship with mortality in critical illness, there is evidence to support administration of corticosteroids to critically ill patients with suspected adrenocortical insufficiency. In the study of Sibbald and colleagues, only one of five patients with septic shock and adrenocortical insufficiency survived.[7] The survivor was the only patient to have received corticosteroid replacement treatment. Furthermore, corticosteroid supplementation improved short-term outcome in patients with adrenocortical insufficiency in septic shock, although mortality was still greater than in patients without adrenocortical insufficiency.[18]

Critical care clinicians should remain vigilant to the possibility of adrenocortical insufficiency. Unfortunately, the literature does not offer a clear biochemical definition in critical illness. Even if such a definition was established, the time delay required to perform an ACTH stimulation test and cortisol assays would probably negate its contribution towards making a clinical decision about commencing corticosteroid treatment. Adrenocortical insufficiency is clinically suspected in patients with rapidly escalating inotropic requirements associated with poor haemodynamic responses. In practice it is likely that corticosteroids would be administered before a biochemical diagnosis could be confirmed.

Most previous studies have used supra-physiological doses of corticosteroids. The well known risks of this may outweigh the benefits of biochemically correcting adrenocortical insufficiency in critical illness. Administration of physiological doses of corticosteroids (cortisol 30 mg daily for adults),[35] aiming for physiological replacement rather than pharmacological treatment, may improve long-term mortality in these patients. Even if physiological doses of corticosteroids prove to be beneficial only transiently in this subset of patients, they may still have a useful role. The resulting improvement in cardiovascular stability in the short-term can only increase the opportunity for other treatments to correct the underlying pathophysiological chaos in critical illness and hopefully reduce mortality.

We feel it is time for a consensus on the definition of adrenocortical insufficiency in critical illness. A similar consensus has been achieved for other conditions.[36] This would standardize future studies and help in the identification of patients who may benefit from corticosteroid treatment. Double-blind, placebo-controlled studies should follow and answer, once and for all, if replacement therapy in this subset of critically ill patients improves outcome. Until then, clinicians should: have an increased index of suspicion for diagnosing adrenocortical insufficiency in the critically ill; measure basal and post-stimulation plasma cortisol concentrations more readily; and consider administration of physiological rather than supra-physiological doses of corticosteroids when adrenocortical insufficiency is suspected.

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CLINICAL INVESTIGATIONS

Effect of graft reperfusion on haemodynamics and gas exchange during liver transplantation†

T. S. WALSH, P. HOPTON, O. J. GARDEN AND A. LEE

Summary

We have documented the changes in gas exchange, haemodynamic state and associated physiological variables which occurred after graft reperfusion in 20 patients undergoing uncomplicated orthotopic liver transplantation. Gas exchange was measured during constant ventilation using a metabolic monitor. After reperfusion, there were increases in $\dot{V}o_2$ (mean increase 57 (SD 25) ml min^{-1}) ($P<0.001$), $\dot{V}co_2$ (mean increase 38 (17) ml min^{-1}) ($P<0.001$) and Pa_{CO_2} (mean increase 0.88 (0.56) kPa) ($P<0.001$). These were associated with increases in cardiac output (1.2 (1.0) litre min^{-1} m^{-2}) ($P<0.001$) and mean pulmonary artery pressure (9 (6) mm Hg) ($P<0.001$). There was a decrease in standard bicarbonate concentration (0.96 (1.6) mmol litre^{-1}) ($P<0.02$) and increase in hydrogen ion concentration (8.15 (5.9) mmol litre^{-1}) ($P<0.001$) consistent with the release of an acid load from the graft and previously ischaemic tissues. The increases in Pa_{CO_2} and hydrogen ion concentration were significantly larger in patients in whom venovenous bypass was used during the anhepatic period compared with the "piggyback" surgical technique. We found correlations between the changes in Pa_{CO_2} and $\dot{V}co_2$ ($r^2=0.25$, $P<0.02$), cardiac output and $\dot{V}co_2$ ($r^2=0.34$, $P<0.01$), and cardiac output and $\dot{V}o_2$ ($r^2=0.34$, $P<0.01$). We conclude that major alterations in gas exchange occur after reperfusion which result from alterations in metabolic rate and haemodynamic changes. These may be clinically relevant, particularly in patients at risk of cerebral oedema. (*Br. J. Anaesth.* 1998; **81**: 311–316).

Keywords: liver, transplantation; cardiovascular system, effects; oxygen, consumption; carbon dioxide, elimination

During orthotopic liver transplantation the point at which reperfusion of the donor graft occurs is associated with rapid physiological and metabolic changes. These include an increase in cardiac output, central venous pressure and pulmonary artery pressure, and a decrease in systemic vascular resistance which, when severe, constitute the post-reperfusion syndrome.[1] The causes of these changes are incompletely understood but probably include a sudden increase in venous return, cardiac reflexes and release of substances from the graft itself, such as proinflammatory cytokines and oxygen free radicals.[2 3] Alterations in metabolic rate also occur as the graft is perfused with oxygenated blood and becomes metabolically active. It has been shown previously that an increase in whole body oxygen consumption occurs after reperfusion which may reflect oxygen uptake by the graft.[4 5]

However, there are no detailed studies on the alterations in gas exchange which accompany this increase or their relationship to haemodynamic changes and acid–base balance. These are important because they may contribute to potentially fatal complications, such as acute intracranial hypertension, which can occur at this time. Our aim was to describe in detail the complex changes in pulmonary and systemic haemodynamics, gas exchange and metabolic rate which occur after reperfusion to provide a rational approach to the management of the physiological changes which occur at this time.

Patients and methods

We studied prospectively 20 patients, mean age 52 (range 21–67) yr, undergoing orthotopic liver transplantation over a 10-month period. In eight patients venovenous bypass from portal and femoral veins to the axillary vein was used during the anhepatic phase. In the remaining 12 patients the "piggyback" technique was used in which inferior vena caval flow is preserved throughout surgery.[6] With this technique a temporary portacaval shunt was constructed during the anhepatic period and a caval to caval anastomosis fashioned between the donor liver and recipient inferior vena cava.

Anaesthesia was maintained with propofol–alfentanil infusion supplemented with midazolam. An infusion of atracurium was used for neuromuscular block and the lungs were ventilated with an air–oxygen mixture using a Servo 900C ventilator. Ventilator settings were adjusted to achieve Pa_{CO_2} 3.5–4.5 kPa early in the operation and were not altered during the study. All patients received dopamine 3 μg kg^{-1} min^{-1} and aprotinin at a rate of 500 000 u. h^{-1} after a loading dose of 2×10^6 u. Arterial, central venous and pulmonary artery pressures were monitored continuously. Cardiac output was measured using an automated thermodilution technique (Baxter Vigilance system, Baxter Healthcare Corp., Irvine, CA, USA). Haemodynamic data were collected con-

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tinuously to computer via the analogue output of the monitors. Fluids and blood products were administered as indicated clinically and after reperfusion, bolus doses of epinephrine (adrenaline) were given to treat hypotension if required. No patient received bicarbonate or other alkali therapy during the study.

Metabolic gas exchange was measured with a Deltatrac metabolic monitor (Datex, Helsinki). This is an open system, indirect calorimeter which has been validated in patients undergoing ventilation and its accuracy assessed in lung models.[7–10] $\dot{V}CO_2$ is measured by drawing all expired gas into a fixed flow generator which entrains air to a total flow rate, usually set at 45 litre min^{-1}. An infrared analyser measures the carbon dioxide fraction in the resulting mixture and $\dot{V}CO_2$ is calculated by multiplying the fractional concentration by the flow rate. The respiratory quotient (RQ) is calculated from the equation:

$$RQ=(1-FI_{O_2})/([FI_{O_2}-FE'_{O_2}]/FE_{CO_2})-FI_{O_2}$$

This equation is derived from the Haldane transformation and enables RQ to be calculated from gas fractions alone on the assumption that all gases other than oxygen and carbon dioxide are in equilibrium. For this reason no volatile anaesthetic agents or nitrous oxide were used. Inspired and expired oxygen and carbon dioxide fractions are measured by paramagnetic and infrared analysers at appropriate points in the system. $\dot{V}O_2$ is derived as $\dot{V}CO_2$/RQ on the assumption that a steady state is present. All data are presented as 1-min averages.

The accuracy of the machine was checked every 3 months according to the manufacturer's recommendations by an alcohol burning test (for RQ) and a flow generator calibration. Before each use the machine was allowed to warm up for 30 min and was then calibrated for atmospheric pressure using an aneroid barometer. A gas calibration was carried out before each measurement against a standard mixture (95% oxygen, 5% carbon dioxide). The machine incorporates a temperature compensation and artefact suppression algorithm and self calibrates during use. Measured gas volumes are expressed at standard temperature and pressure. All data were collected every 1 min to computer using software supplied by the manufacturer.

In each patient an arterial blood sample was obtained as part of our routine perioperative monitoring before and approximately 30 min after reperfusion. Samples were processed within 5 min of collection using an IL BGE 1400 series analyser which was checked daily using a quality control sample. The quoted resolution of the machine is 0.01 kPa for Pa_{O_2}, 0.01 kPa for Pa_{CO_2} and 0.1 nmol litre^{-1} for H^+ concentration. Five-minute averages for all haemodynamic data and metabolic data were calculated retrospectively at the time of blood sampling in each patient. From these data the following derived variables were calculated before and after reperfusion:

Mixed expired carbon dioxide pressure $(P\bar{E}_{CO_2})=(PB_{atm}-SVP(H_2O))\times FE_{CO_2}$ where PB_{atm}=barometric pressure and SVP(H_2O)= saturated vapour pressure of water at 37°C.

Pulmonary deadspace ratio $(VD/VT)=(PA_{CO_2}-P\bar{E}_{CO_2})/PA_{CO_2}$ where PA_{CO_2}, alveolar carbon dioxide pressure, is assumed to equal Pa_{CO_2}.

Alveolar ventilation $(\dot{V}A)=(\dot{V}CO_2\times 95)/PA_{CO_2}$.

Alveolar oxygen pressure $(PA_{O_2})=FI_{O_2}-SVP(H_2O)-PA_{CO_2}/RQ$.

Alveolar to arterial oxygen tension gradient (A–a gradient)$=PA_{O_2}-Pa_{O_2}$.

Data were processed using the Fig P for Windows and Minitab statistical packages. Differences between physiological variables before and after reperfusion were compared using the Student's paired *t* test. The relationship between changes in physiological variables at reperfusion was investigated by calculating the Pearson product moment correlation coefficient. $P<0.05$ was considered statistically significant.

Results

The indications for surgery were as follows: primary biliary cirrhosis (eight patients), primary sclerosing cholangitis (three patients), alcoholic cirrhosis (four patients), chronic rejection of liver transplant (two patients) and fulminant hepatic failure (three patients). No patients suffered cardiac arrhythmias at reperfusion and there were no cases of primary graft non-function. All patients had successful transplants and were alive at 1 month. Mean time of blood sampling after reperfusion was 28 (SD 11) min. Continuous monitoring of metabolic gas exchange revealed increases in $\dot{V}O_2$ and $\dot{V}CO_2$ which consistently occurred within 2–3 min of graft reperfusion (fig. 1). Changes in physiological variables at reperfusion are summarized in table 1.

Boluses of epinephrine were required after reperfusion to maintain arterial pressure in 16 patients. The maximum dose required in any patient was 0.8 mg and no patient required infusions of epinephrine or other inotropic drugs. There was no correlation between epinephrine use and haemodynamic or gas exchange changes.

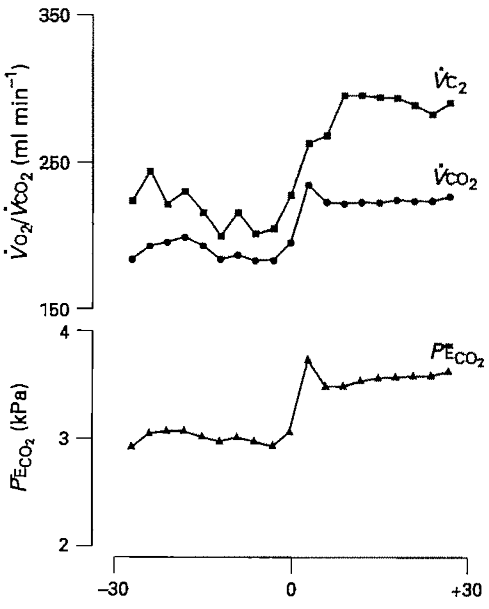

Figure 1 Typical example of changes in oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide elimination ($\dot{V}_{CO_2}$) and mixed expired carbon dioxide partial pressure ($P\bar{E}_{CO_2}$) after reperfusion in an individual patient during constant ventilation. Significant increases in all three variables were observed within 5 min of opening the vascular clamps and perfusing the graft. These typically reached a plateau within 10 min after which only minor fluctuations occurred.

Table 1 Comparison between haemodynamic variables, metabolic gas exchange and associated physiological variables before and after graft reperfusion. All values are mean (SD). MAP=mean arterial pressure; MPAP=mean pulmonary artery pressure; $\dot{V}_{CO_2}$=carbon dioxide elimination; RQ=respiratory quotient; $\dot{V}_{O_2}$= oxygen consumption; $F_{I_{O_2}}$=inspired oxygen fraction; Pa_{O_2}=arterial oxygen tension; $P_{A_{O_2}}$=alveolar partial pressure of oxygen; A–a gradient=alveolar to arterial oxygen tension gradient; Pa_{CO_2}=arterial carbon dioxide tension; $P\bar{E}_{O_2}$=mixed expired carbon dioxide partial pressure; V_D/V_T=deadspace ratio; $\dot{V}_A$=alveolar ventilation. *$P<0.05$, **$P<0.01$, ***$P<0.001$

	Before reperfusion	After reperfusion	Change
Cardiac output (litre $min^{-1}m^{-2}$)	4.6 (1.3)	5 9 (1.5)	1.2 (1.0)***
MAP (mm Hg)	74 (13)	70 (15)	–4 (15)
MPAP (mm Hg)	15 (4)	24 (6)	9 (6)***
$\dot{V}CO_2$ (ml min^{-1} m^{-2})	138 (30)	176 (37)	38 (17)***
RQ	0.87 (0.12)	0.82 (0.10)	–0.05 (0.09)*
$\dot{V}O_2$ (ml min^{-1} m^{-2})	160 (32)	217 (46)	57 (25)***
$F_{I_{O_2}}$	0.46 (0.09)	0.46 (0.09)	0
Pa_{O_2} (kPa)	25.7 (6.75)	21.79 (6.38)	–3.86 (5 31)**
$P_{A_{O_2}}$(kPa)	38.51 (9.01)	37.23 (9.17)	–1.28 (0.84)***
A–a gradient (kPa)	12.86 (5.99)	15.44 (8.02)	2.58 (5.58)
Pa_{CO_2}(kPa)	4.40 (0.73	5.27 (0.90)	0.88 (0.56)***
$P\bar{E}_{O_2}$(kPa)	2.21 (0.31)	2.78 (0.37)	0 57 (0.23)***
V_D/V_T	0 49 (0.06)	0.46 (0.09)	–0.03 (0.05)**
$\dot{V}_A$ (litre min^{-1})	3.02 (0.62)	3.23 (0.70)	0.22 (0.27)**
H^+ concentration (nmol $litre^{-1}$)	44.8 (9.6)	52.8 (9.9)	8.15 (5.9)***
Standard bicarbonate (mmol $litre^{-1}$)	20.8 (2.9)	19.9 (2.4)	–0.96 (1.6)*

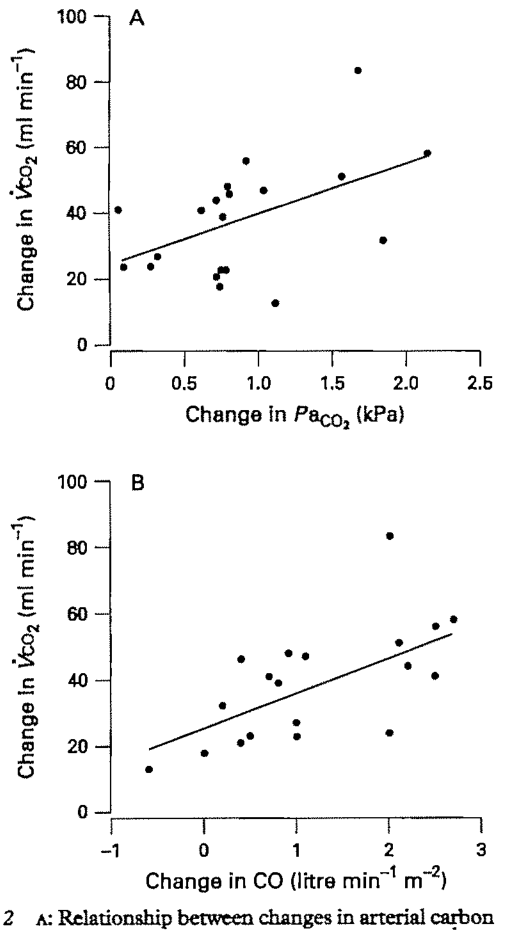

Figure 2 A: Relationship between changes in arterial carbon dioxide tension (Pa_{CO_2}) and carbon dioxide elimination ($\dot{V}_{CO_2}$) at reperfusion. B: Relationship between changes in cardiac output (CO) and $\dot{V}_{CO_2}$ at reperfusion.

We compared the physiological changes which occurred in patients transplanted using either venovenous bypass or piggyback surgical techniques. In patients transplanted using the piggyback technique, the increase in Pa_{CO_2} and hydrogen ion concentration was less than with venovenous bypass (Pa_{CO_2}: piggyback mean increase 0.61 (SD 0.41) kPa *vs* venovenous bypass 1.3 (0.53) kPa ($P<0.02$); hydrogen ion concentration: piggyback mean increase 5.6 (5.5) mmol $litre^{-1}$ *vs* venovenous bypass 11.7 (4.6) mmol $litre^{-1}$) ($P<0.02$)). Changes in the other measured variables were similar.

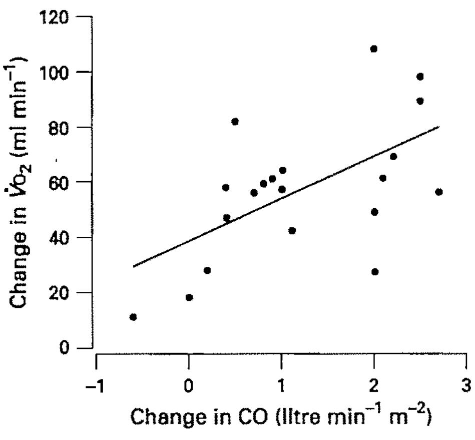

Figure 3 Relationship between changes in cardiac output (CO) and oxygen consumption ($\dot{V}_{O_2}$) at reperfusion.

There were significant correlations between changes in Pa_{CO_2} and $\dot{V}CO_2$ ($r^2=0.25$, $P<0.02$), cardiac output and $\dot{V}CO_2$ ($r^2=0.34$, $P<0.01$), and cardiac output and $\dot{V}O_2$ ($r^2=0.34$, $P<0.01$) (figs 2, 3).

Discussion

The principal finding of our study was that reperfusion of the donor graft during liver transplantation was associated with marked changes in gas exchange and metabolic rate. We observed clinically significant increases in $\dot{V}O_2$ and $\dot{V}CO_2$ which occurred within minutes of removing the vascular clamps and restoring blood supply to the graft. These changes occurred in association with the well-established observation that cardiac output and pulmonary artery pressure increase at reperfusion while systemic vascular resistance decreases.[1 11 12]

The accuracy of physiological measurements made during a period of rapid change was an important consideration in this study. The validity of thermodilution measurements of cardiac output is decreased by rapid changes or fluctuations in blood temperature, and rapid infusion of i.v. fluids,[13] both of which occur frequently at the time of reperfusion. We did not analyse data in the immediate period after reperfusion, and used an automated method of determining cardiac output which has the advantage of eliminating operator error and averaging multiple data points. Bottiger and colleagues[14] showed that the agreement between this method and conventional bolus thermodilution was good during liver transplantation if approximately 30 min had elapsed from reperfusion. Therefore, we consider it unlikely that large errors occurred in measurements of cardiac output in our patients.

The Deltatrac metabolic monitor has been used widely to measure $\dot{V}O_2$ in critically ill patients, and during stable laboratory simulations has an accuracy of approximately ±4% for $\dot{V}O_2$ and ±3% for $\dot{V}CO_2$.[4 5] Accuracy is reduced in the presence of a high or fluctuating F_{IO_2}, anaesthetic gases or the presence of gas leaks in the circuit, but these were not relevant in this study. The machine calculates $\dot{V}O_2$ from $\dot{V}CO_2$ and RQ on the assumption that the patient is at steady state, an approach used to avoid the inaccuracies associated with measuring gas volumes in patients undergoing ventilation. We did not alter ventilation during the study, but the significant changes in cardiac output, acid–base status and deadspace ratio which we observed represented disruptions to steady state which may have influenced the validity of $\dot{V}O_2$ estimations. Inaccuracy attributable to these factors should decline exponentially with time as a new equilibrium is established after reperfusion. Our data indicate that devices which assume the presence of a steady state when determining $\dot{V}O_2$ after graft reperfusion may be inaccurate until an equilibrium has been re-established. The time required for this to occur is unknown and is likely to vary between patients. After changes in ventilation the majority of this process occurs within 20 min[15 16] and it is likely that errors attributable to haemodynamic, acid–base and deadspace changes were small 30 min after reperfusion assuming the patients were otherwise stable. This conjecture was supported by our observation that $\dot{V}O_2$ reached a plateau within 10–15 min, and did not fluctuate significantly in the majority of patients (fig. 1).

The increase in Pa_{CO_2} has several explanations. First, increased aerobic metabolism by the graft resulted in an increase in carbon dioxide production that was not compensated for by increased ventilation, which we intentionally left unchanged. Second, the small decrease in standard bicarbonate concentration indicated an acute metabolic acidosis which probably resulted from the release of an acid load from the graft and other ischaemic tissues. Welte and colleagues[17] found that gastric intramucosal pH decreased during the anhepatic phase of liver transplantation which was consistent with the presence of gut ischaemia, and this resolved after reperfusion. In our patients there was no correlation between the changes in standard bicarbonate or hydrogen ion concentration and Pa_{CO_2} which may indicate that buffering of the acid load was not a major determinant of the change in Pa_{CO_2}. Impaired elimination of carbon dioxide may have contributed to the increase in Pa_{CO_2}, but despite constant ventilator settings, we observed a small but significant decrease in deadspace ratio and an increase in alveolar ventilation, which would augment rather than impair carbon dioxide elimination. The most likely explanation for these changes was increased pulmonary perfusion and a decrease in the $\dot{V}/\dot{Q}$ ratios of non-dependent alveoli, attributable to increased pulmonary artery pressure and cardiac output.

The observed increase in $\dot{V}CO_2$ after reperfusion correlated with the increase in Pa_{CO_2}. This association was expected under conditions of constant ventilation where, in the absence of severe pulmonary disease, alveolar and arterial PCO_2 are almost identical.[15] Our results also indicate that altered pulmonary blood flow is an important determinant of $\dot{V}CO_2$ because we found a strong correlation between changes in cardiac output and $\dot{V}CO_2$. This observation is consistent with those made by Shibutani and coworkers[18] in patients undergoing aortic aneurysm surgery in whom decreases in $\dot{V}CO_2$ correlated strongly with decreases in cardiac output.

An increase in arterial carbon dioxide tension causes vasodilatation.[15] In patients with acute respiratory distress syndrome, Thorens and colleagues showed that acute hypercapnia, induced over 30–60 min by a reduction in minute ventilation, increased cardiac output and pulmonary artery pressure, and decreased systemic vascular resistance.[19] Although many factors may be important, the similarity between these changes and those occurring in our patients suggest that altered carbon dioxide tension may contribute to the haemodynamic changes which occur after reperfusion during liver transplantation.

A possible clinical relevance of altered carbon dioxide metabolism relates to cerebral blood flow in patients with abnormal cerebral autoregulation or intracranial hypertension, both of which are common in patients undergoing liver transplantation for fulminant hepatic failure. Cerebral oedema and increased intracranial pressure have also been described recently in patients with chronic liver disease.[20] In patients with cerebral oedema, sudden increases in intracranial pressure are well recognized after reperfusion and may lead to coning and death. The exact aetiology of these changes is unclear and is probably multifactorial, but cerebral vasodilatation in response to increased arterial carbon dioxide tension is a possible contributing factor. The cerebrovascular response to acute hypercapnia in patients with normal autoregulation is extremely rapid (<10 s).[21] Our data indicate that an increase in minute ventilation is advisable before reperfusion to minimize the risk of carbon dioxide-induced cerebral vasodilatation in patients at risk of cerebral complications.

We found that Pa_{CO_2} and hydrogen ion concentration increased less in patients transplanted using the piggyback technique. Steib and colleagues found that cardiac output and oxygen delivery were higher during the anhepatic phase of transplantation with the piggyback technique compared with venovenous bypass[22] and we have made similar unpublished observations. Better organ perfusion, particularly of splanchnic tissues, during the anhepatic phase of transplantation may account for the smaller acid load released into the systemic circulation at reperfusion with the piggyback technique.

There was a strong relationship between changes in cardiac output and $\dot{V}O_2$ after reperfusion. There are two possible explanations for this: first, $\dot{V}O_2$ may be supply-dependent at this time, particularly if the increase in cardiac output improves oxygen delivery to tissues which were ischaemic during the anhepatic period.[24] Alternatively, oxygen uptake by the new liver resulting in increased oxygen demand may be the major determinant of cardiac output, and therefore oxygen delivery, after reperfusion. Previous studies have suggested that the change in $\dot{V}O_2$ at reperfusion is a clinically useful measure of graft function.[4 5 24] However, several factors could influence $\dot{V}O_2$ at this time. In particular, if the change in $\dot{V}O_2$ is attributable in part to factors other than metabolism of the graft, such as epinephrine use and oxygen debt in splanchnic tissues incurred during the anhepatic phase, the sensitivity and specificity of this test are unlikely to be high. This may explain why some authors have observed a large increase in $\dot{V}O_2$ in patients in whom primary liver non-function occurred.[25]

In most patients the increase in $\dot{V}O_2$ was slightly larger than the increase in $\dot{V}CO_2$ and this was reflected by a small but statistically significant decrease in RQ. A similar observation was made by Svensson and colleagues[4] and it is possible that this occurred because of altered substrate utilization at the tissue level, such as restoration of hepatic lipolysis. An alternative explanation is that the excess oxygen consumption was caused by free radical formation, which consumes oxygen without the production of carbon dioxide. Free radical production has been demonstrated after reperfusion, may continue for up to 24 h, and has been implicated in the process of reperfusion injury.[26 27] Indirect evidence that this occurs also comes from work demonstrating acute depletion of plasma antioxidants after reperfusion.[28]

Despite significant changes in pulmonary artery pressure and blood flow, the A–a oxygen tension gradient, a measure of physiological shunt, did not change in the majority of patients. We observed small decreases in $P\text{A}_{\text{O}_2}$ and $P\text{a}_{\text{O}_2}$ which were largely explained by the increase in $P\text{a}_{\text{CO}_2}$ and which were not clinically important in our patients. These changes may become relevant in patients with limited physiological reserve because of coexisting pulmonary disease, which occurs in both chronic and acute liver disease.[29 30] However, our data indicate that routine use of high inspired oxygen fractions at reperfusion, which was suggested in a recent review, is unnecessary[2]. Indeed, the use of high inspired oxygen fractions increases lung atelectasis during anaesthesia.[31]

In summary, we have documented the changes in carbon dioxide and oxygen kinetics which occur at reperfusion during uncomplicated liver transplantation. These include significant increases in $\dot{V}O_2$, $\dot{V}CO_2$ and $P\text{a}_{\text{CO}_2}$ which occur because of oxygen uptake by the new liver, and the perfusion of tissues which were ischaemic during the anhepatic period. The magnitude of these changes may be clinically relevant, particularly in the high risk patient in whom cerebral and haemodynamic instability may occur.

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Factors affecting assessment of cerebral autoregulation using the transient hyperaemic response test†

G. CAVILL, E. J. SIMPSON AND R. P. MAHAJAN

Summary

The transient hyperaemic response in the middle cerebral artery blood flow velocity on the release of brief compression of the ipsilateral common carotid artery has been validated as an indicator of cerebral autoregulation. We evaluated, in three stages, the effect of experimental factors such as duration of compression of the common carotid artery and magnitude of the decrease in blood flow velocity during common carotid artery compression on the transient hyperaemic response. In stage 1, 13 healthy volunteers underwent six transient hyperaemic response tests each; two tests each for either 3, 6 or 10 s duration of compression of the common carotid artery. In stage 2, 10 volunteers underwent four transient hyperaemic response tests each; two tests each for either 10 or 15 s duration of compression of the common carotid artery. In stage 3, data from the transient hyperaemic response tests using 10 s compression from the 23 volunteers who participated in stages 1 and 2 were analysed to evaluate the relationship between magnitude of decrease in blood flow velocity at the onset of compression and the transient hyperaemic response. The transient hyperaemic response ratio (blood flow velocity after the release of compression/baseline blood flow velocity) increased significantly when the duration of common carotid artery compression increased from 3 to 6 s, or from 6 to 10 s (stage 1); increase in the duration from 10 to 15 s did not have any significant effect (stage 2). The transient hyperaemic response ratio correlated significantly with the magnitude of decrease in blood flow velocity after compression, up to the values of the compression ratio (percent decrease in blood flow velocity at the onset of compression) of 40% but not more (stage 3). We conclude that experimental factors such as duration of common carotid artery compression and magnitude of the decrease in blood flow velocity during common carotid artery compression can significantly influence the transient hyperaemic response. These factors should be controlled if the transient hyperaemic response test is used for a comparison between repeated measurements. A compression time of 10 s and a compression ratio of 40% or more, allow maximum expression of the hyperaemic response in healthy volunteers. (*Br. J. Anaesth.* 1998; **81**: 317–321.)

Keywords: brain, blood flow; measurement techniques, Doppler ultrasonography

Introduction of transcranial Doppler ultrasonography has prompted the development of non-invasive techniques of assessing cerebral autoregulation.[1–3] These techniques use different methods of modulating cerebral perfusion pressure, including the use of vasoactive agents,[1] cuffs around the thigh[2] and short-lasting compression of the common carotid artery.[3] For the purpose of research in anaesthesia, the technique should be simple, reproducible, quantifiable and preferably devoid of the use of vasoactive agents.

The transient hyperaemic response test involves the use of transcranial Doppler ultrasonography to establish a continuous record of blood flow velocity in the middle cerebral artery and then briefly compressing the ipsilateral common carotid artery. If autoregulation is effective, the reduction in middle cerebral arterial pressure after common carotid artery compression should cause vasodilatation in the arterioles distal to the middle cerebral artery. Therefore, release of the compression would result in a transient increase in cerebral blood flow (CBF), and thus middle cerebral artery blood flow velocity (fig. 1).[3–5] This technique is simple and does not involve the use of vasoactive agents and, therefore, may prove to be a useful research tool.

Smielewski and colleagues[6] have shown that the transient hyperaemic response ratio (THRR: ratio of hyperaemic blood flow velocity after release of compression to baseline blood flow velocity) is a valid index of cerebral autoregulation and has similar sensitivity to the leg-cuff method, as described by Aaslid and colleagues,[2] in detecting the changes in cerebral autoregulation produced by different systemic carbon dioxide concentrations. In theory, both the duration of common carotid artery compression and magnitude of the decrease in blood flow velocity at the onset of compression can affect the transient hyperaemic response.[4 7] To date there are insufficient data examining the effect of these experimental factors on THRR. In this study, we have evaluated the effects of duration of compression and the magnitude of the decrease in blood flow velocity at the onset of compression on THRR.

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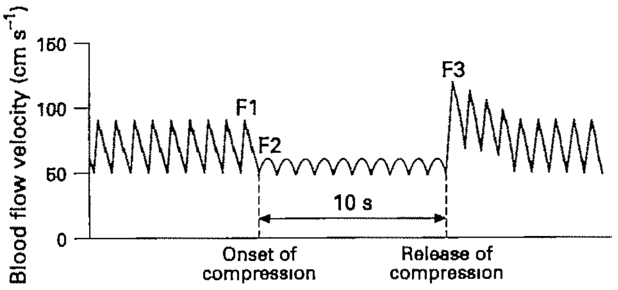

Figure 1 Diagrammatic representation of the transient hyperaemic response in the middle cerebral artery after release of a brief compression of the ipsilateral common carotid artery.

Subjects and methods

The study was approved by the Medical School Ethics Committee. All volunteers were healthy non-smokers and free from systemic or vascular problems. Bilateral carotid artery sonograms were performed in each volunteer to exclude atheromatous disease.

Volunteers were studied in the supine position with the head resting on a pillow. The left middle cerebral artery was identified by recognition of the characteristic waveform, typical flow velocity profile and depth of insonation using a 2-MHz pulsed transcranial Doppler probe (SciMed PCDop 842).[6] After establishing a stable and continuous record of blood flow velocity in the middle cerebral artery, the position of the transcranial Doppler probe was fixed using a headband. Transcranial Doppler measurements were recorded on a DAT tape for subsequent analysis using specific software (SciMed PCDop 842). Simultaneous continuous measurements of finger arterial pressure and heart rate were made using an automated pressure cuff (Finapres, Ohmeda 2300). Changes in arterial pressure or heart rate were considered significant if at any stage during the transient hyperaemic response test their value was outside the normal range recorded during 10 s of baseline measurements.

STAGE 1

We studied 13 volunteers (seven men, aged 21–39 yr). Six transient hyperaemic response tests were performed in each; two tests each for either 3, 6 or 10 s duration of compression of the common carotid artery. At least 2 min were allowed between tests and the duration of compression was selected randomly.

STAGE 2

Ten volunteers (six men, aged 23–33 yr) underwent four transient hyperaemic response tests each; two tests each for either 10 or 15 s duration of common carotid artery compression. At least 2 min were allowed between tests and the duration of compression was selected randomly.

STAGE 3

A transient hyperaemic response test was accepted only: (a) when onset of compression resulted in a sudden and maximal decrease in blood flow velocity; (b) when conditions remained stable during compression; and (c) when flow transients after release of compression (associated with inertial or volume compliance[8]) were not obvious. If any of these confounding factors were detected, the test was repeated 2 min later. In stage 3, the data collected from stages 1 and 2 were used. Transient hyperaemic response tests, which were performed with 10 s of common carotid artery compression in all the volunteers who participated in stages 1 and 2, were selected for analysis. The magnitude of the decrease in blood flow velocity at the onset of compression was correlated with the transient hyperaemic response.

DATA HANDLING AND STATISTICAL ANALYSIS

For the analysis, the middle cerebral artery waveform just preceding common carotid artery compression (F1), the first waveform after the onset of common carotid artery compression (F2) and the first waveform after release of common carotid artery compression (F3) were selected. PCDop has analogue outputs of flow velocity maximum (*v*max), determined using the upper envelope of the velocity power spectrums. The time averaged mean of *v*max was used for analysis.

THRR was calculated using the formula[6]:

$$\text{THRR} = \text{F3/F1} \qquad (1)$$

As a measure of the magnitude of the decrease in blood flow velocity during compression, the compression ratio (CR) was calculated using the formula[6]:

$$\text{CR}(\%) = (\text{F1}-\text{F2}).100/\text{F1} \qquad (2)$$

The mean of the two measurements at each duration of compression was used. For stage 1, the Kruskal–Wallis test was applied to THRR, CR and baseline values of blood flow velocity, heart rate and mean arterial pressure recorded during the transient hyperaemic response tests with different durations of compression. The Wilcoxon signed rank test was used to compare THRR after a duration of compression of 3 s *vs* 6 s, and 6 s *vs* 10 s in stage 1, and 10 s *vs* 15 s in stage 2. For stage 3, Pearson correlation and regression analysis between CR and THRR were applied to the data from transient hyperaemic response tests of 10 s duration of compression from stages 1 and 2.

Results

MAP and heart rate did not change significantly during any transient hyperaemic response test.

STAGES 1 AND 2

Baseline values for heart rate, mean arterial pressure, blood flow velocity and CR were comparable at different durations of common carotid artery compression (table 1). In stage 1, duration of compression had a significant effect on THRR (P=0.002, Kruskal–Wallis). This index increased significantly as the duration of compression was increased from 3 to 6 s (P=0.008, Wilcoxon signed rank test), or from 6 to 10 s (P=0.004, Wilcoxon signed rank test) (fig. 2, table 1). In stage 2, increasing the duration from 10

Table 1 Median (25–75% quartiles) heart rate (HR), mean arterial pressure (MAP), compression ratio (CR), baseline middle cerebral artery flow velocity (FV) and the transient hyperaemic response ratio (THRR). Wilcoxon signed-rank test: $^{**}P<0.01$ compared with 3 s of compression; $^{\dagger\dagger}P<0\ 01$ compared with 6 s of compression

	Duration of compression				
	Stage 1, n=13			Stage 2, n=10	
	3 s	6 s	10 s	10 s	15 s
HR (beat min^{-1})	70.0 (67.0–77.5)	72.0 (66.0–74.5)	70.0 (66.5–76.5)	70.0 (64.0–76.2)	70.0 (63.5–73 2)
MAP (mm Hg)	94.0 (87.5–98.0)	92. 0 (88.5–94.5)	95.0 (87.5–97.5)	91.0 (86 7–96.5)	90.0 (82.7–93.2)
FV (cm s^{-1})	54.0 (52.5–60.5)	57.0 (50.5–59.0)	57.0 (51.0–60.0)	54.5 (51.0–57.5)	54 5 (51.5–57.2)
CR (%)	34.0 (25.5–55.0)	35.0 (24.0–51.0)	36.0 (26.0–52.0)	60.5 (46.0–65.5)	57.5 (43.0–66.2)
THRR	1.17 (1.11–1 23)	1.23** (1.17–1.28)	1.35†† (1.26–1.38)	1.42 (1.40–1.43)	1.40 (1.37–1.44)

to 15 s did not have any significant effect on THRR (fig. 3, table 1).

STAGE 3

A total of 23 volunteers underwent transient hyperaemic response tests with a 10 s duration of common carotid artery compression. CR was 14–75% and THRR 1.10–1.46. Both variables showed a significant positive correlation (r^2=0.7, $P<0.001$) (fig. 4). However, the increase in THRR tended to plateau as the value of CR approached 40%. Pearson correlation analysis on the subsets of data showed a significant correlation (r^2=0.9, n=10, $P<0.001$) between THRR and CR ≤40% but not between THRR and CR >40% (n=13, r^2=0.1, P=0.29).

Discussion

Giller[3] described the transient hyperaemic response test as a bedside investigation for assessment of cerebral autoregulation. Subsequently, a modelling study[4] was published followed by a clinical study involving a large number of patients with neurological disorders,[5] further demonstrating the usefulness of this test in a clinical setting. Only recently have Smielewski and colleagues[6] validated THRR as an index of cerebral autoregulation compared with the autoregulatory index obtained by the leg-cuff method described by Aaslid and colleagues.[2] They have shown this test to be simple, sensitive, reproducible and therefore potentially an attractive research tool.[6 9]

Our results showed that both duration of compression and the magnitude of the decrease in blood flow velocity during compression affected THRR. These findings have important implications because control of these factors would be necessary if the test is used to compare cerebral autoregulation between different individuals or between repeated measurements in an individual.

DURATION OF COMPRESSION

Cerebral autoregulation is a complex process involving several mechanisms which operate at different rates.[10–12] Experiments have shown an initial fast component of cerebral autoregulation.[13–16]

Transcranial Doppler studies have confirmed the presence of fast autoregulation which occurs within 5–8 s of a step decrease in arterial pressure.[2] A modelling study of the transient hyperaemic response has suggested that compression should be maintained for longer than the inherent autoregulation delay (5–8 s) in order to generate a constant response.[4] Our results support this theoretical suggestion and show that a compression time of 10 s

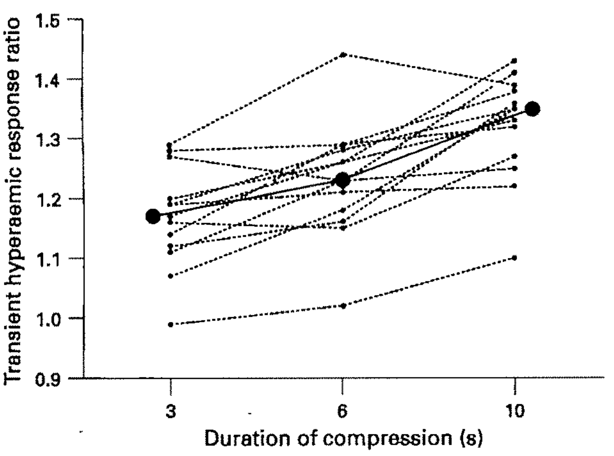

Figure 2 Effect of duration of compression of the common carotid artery on the transient hyperaemic response ratio (THRR) in stage 1. Dotted lines represent individual subjects; solid line represents median change.

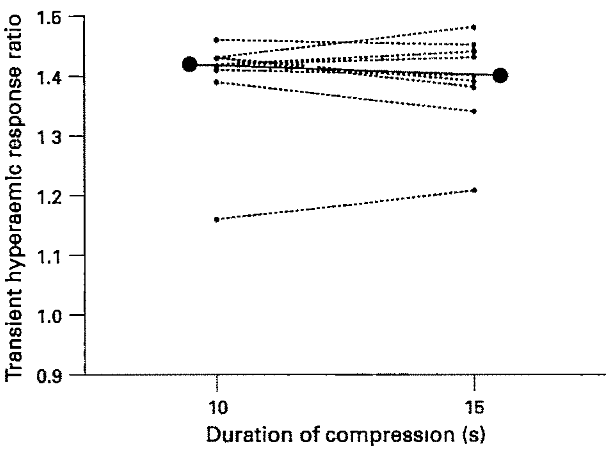

Figure 3 Effect of duration of compression of the common carotid artery on the transient hyperaemic response ratio (THRR) in stage 2. Dotted lines represent individual subjects; solid line represents median change.

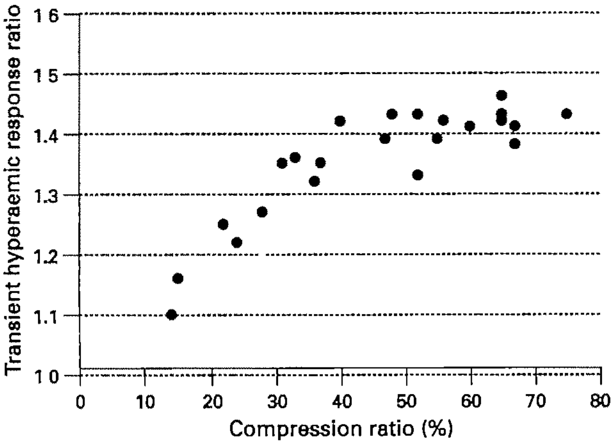

Figure 4 Relationship between the compression ratio (CR) and the transient hyperaemic response ratio (THRR). The increase in THRR tends to plateau as the value of CR reaches 40%. Overall correlation is significant (r^2=0.7, P<0.001).

would fulfil the criteria. Our study has not shown any advantage of increasing the duration of compression from 10 s to 15 s. Smielewski and colleagues[6] attempted to evaluate the effect of duration of compression on the transient hyperaemic response. They concluded that the result of the transient hyperaemic response test is independent of compression time, providing the compression lasts for at least 5 s. Our results indicate that a compression time of 5 s may not be sufficient for complete expression of the transient hyperaemic response, and in fact Smielewski and colleagues[6] showed an increased response after up to 7 s of compression which was not significant, probably because of increased variability. In addition, our results showed that the inherent autoregulatory delay in human volunteers may last 6–10 s, and that a compression time of 10 s would ensure maximal response.

Potentially, changes in resting arterial pressure, CR (see below) and end-tidal carbon dioxide concentration can confound the results obtained by a transient hyperaemic response test.[4 6 7] In stages 1 and 2, resting arterial pressure and CR did not change significantly during different durations of compressions within an individual (table 1). Although we did not measure end-tidal carbon dioxide concentration in our volunteers, it is highly unlikely that it would have changed significantly between different tests as all tests were performed under the same resting conditions. We allowed 2 min between successive measurements. This decision was based on a preliminary study which had shown that the results of the transient hyperaemic response test were reproducible even if 10 repeated measurements at 2-min intervals were made.[17] Measurement of THRR and CR is based on single pulse wave tracings before, during and after compression. In order to avoid artefacts we accepted the transient hyperaemic response test for analysis only when it met strict criteria, such as absence of flow transients[8] and unchanged reflected Doppler power[2] during the test.

EFFECT OF CR

Contrary to our findings, Smielewski and colleagues[6] concluded that CR had no effect on the size of the transient hyperaemic response. The transient hyperaemic response test is based on the principle that brief occlusion of the common carotid artery causes a decrease in blood flow velocity at the ipsilateral circle of Willis which provokes autoregulatory mechanisms.[4] Provided that compression achieves total occlusion of the common carotid artery, the magnitude of the decrease in blood flow velocity in the middle cerebral artery during compression (CR) is dependent on the effectiveness of the collateral circulation at the circle of Willis. Because of the heterogeneity of the anatomy of the circle of Willis, CR is likely to vary between different individuals,[4] and is unlikely to be within the control of the investigator. In theory, the decrease in flow velocity at the onset of compression is accompanied by a proportional decrease in perfusion pressure in the middle cerebral artery.[3 4] If autoregulation is intact, the magnitude of the decrease in perfusion pressure would affect the magnitude of change in the resistance of the vascular bed distal to the middle cerebral artery. This, in turn, would affect the magnitude of the transient hyperaemic response after release of compression.[4] However, this would hold true only as long as the reduced pressure in the middle cerebral artery at the time of compression remained greater than the lower limit for autoregulation.[7 18] If compressions are such that the resultant perfusion pressure in the middle cerebral artery is less than the lower limit for autoregulation, the magnitude of CR is unlikely to be related to the size of the transient hyperaemic response. This is because the vascular bed would be unable to respond to decreases in the perfusion pressure beyond the lower limit for autoregulation.

Values for CR in the study of Smielewski and colleagues were 36–57%.[6] Assuming normal arterial pressure in all volunteers (MAP 90–100 mm Hg), CR values of 36–57% would equate to a reduced middle cerebral arterial pressure of approximately 40–64 mm Hg during compression. This would imply that at the onset of compression almost all volunteers in that study had middle cerebral arterial pressures at or below the lower limit for autoregulation (usually 60 mm Hg). This has been suggested as the reason for the lack of correlation between CR and THRR in that study.[18] It has also been suggested that in order to evaluate the effect of CR on THRR, a study should include data from transient hyperaemic response tests in which CR is such that the resultant perfusion pressure in the middle cerebral artery during compression is greater than the lower limit for autoregulation.[18] This would approximate to a CR value of less than 40% in a normotensive subject. Of the 23 volunteers in our study, 10 had CR values of less than or equal to 40%. We have shown that CR has a significant positive correlation with THRR. Our result supports the theoretical modelling of the transient hyperaemic response[4] although it disagrees with previous work[6]. However, we have found that the relationship between CR and THRR starts to plateau when CR exceeds 40%. We postulate that during a transient hyperaemic response test, a CR value of 40% or more approximates to the point at which the autoregulatory capacity is tested to its maximum in a normotensive human volunteer. However, the exact point is likely to vary with the resting arterial pressure and the individual's lower limit for autoregulation.

THRR measures the haemodynamic response to an unquantified stimulus. Therefore, previous workers have used the transient hyperaemic response test in a *qualitative* manner only,[3 5 6] with a THRR of less than 1.09 indicating poor autoregulation. Modelling studies have suggested that it is possible to apply this test for the quantitative assessment of autoregulation.[4 7] This requires control over various factors which can influence the hyperaemic response, especially if the transient hyperaemic response test is applied to make comparative assessments of cerebral autoregulation. Based on the results of our study, we recommend that the duration of compression should be controlled and maintained for 10 s. In addition, the compression ratio should be recorded for each test and its influence on THRR should be taken into consideration, particularly when CR is less than 40%. In theory, resting arterial pressure and the lower limit for autoregulation can also influence the hyperaemic response. Even though the effects of these factors on the transient hyperaemic response have not been studied in experimental or clinical settings, it would seem prudent to achieve a strict control over arterial pressure while making comparisons between different transient hyperaemic response tests.

In summary, we have shown that both the duration of common carotid artery compression and the magnitude of the decrease in blood flow velocity during compression can affect the hyperaemic response. A compression time of 10 s and a CR of more than 40% ensure maximal THRR in normotensive healthy volunteers.

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Influence of dose of domperidone on the acute ventilatory response to hypoxia in humans

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Summary

We have studied the ventilatory responses to acute isocapnic hypoxia (Sp_{O_2} 78.8 (SD 1.4)% for 10 min) in 10 male volunteers given three different doses of oral domperidone: placebo, domperidone tablets 10 mg, 20 mg or 30 mg every 8 h for 48 h on separate days. Neither baseline ventilation nor the acute hypoxic ventilatory response was significantly different from placebo for any of the domperidone doses. However, hypoxic responses were either increased with increments of domperidone or subjects were not sensitive. We arbitrarily divided subjects into two groups according to their hypoxic response–plasma domperidone concentration relationship. Analysis of subjects (n=5) who demonstrated at least a 2-litre min^{-1} increase in ventilation per 10 ng ml^{-1} increase in plasma domperidone concentration showed the greatest augmentation of hypoxic responses with the 20-mg dose (median 19.45 (range 13.37, 22.30) litre min^{-1}) compared with placebo (median 8.21 (3.74, 9.47)) (P=0.003). We were unable to predict which subjects would be sensitive to the effects of domperidone. (*Br. J. Anaesth.* 1998; **81**: 322–326).

Keywords. hypoxia; pharmacology, domperidone; ventilation, hypoxic response

The carotid bodies mediate the ventilatory response to hypoxia in humans. Dopamine, the predominant catecholamine found in human carotid bodies,[1] appears to be involved in the chemotransduction of this effect.[2] In animals, administration of dopamine decreases ventilation and peripheral chemoreceptor activity.[3 4] Infusions of low-dose dopamine in humans also depress the ventilatory response to hypoxia[5 6] and this effect may be prevented by droperidol, a non-specific dopamine antagonist.[7] However, as droperidol is able to cross the blood–brain barrier, a central effect cannot be excluded.

Dopamine receptors in the carotid bodies are of the D2 subtype[8] and domperidone is a specific D2 receptor antagonist which does not readily cross the blood–brain barrier.[9] Although it has a variable effect on baseline normoxic ventilation, it increases the ventilatory response to hypoxia.[2 10 11] In a previous study,[12] we confirmed that oral domperidone increased the hypoxic ventilatory response and offset depression of the initial phase of the hypoxic response caused by 0.1 MAC of isoflurane. In that study, we used a fixed dose of domperidone and found wide variations in plasma concentrations of domperidone. There was no clear relationship between plasma domperidone concentration and the degree of augmentation of the hypoxic response, perhaps because the hypoxic response varied between subjects.

In this study, we determined, within individual subjects, the effect of domperidone dose on the potentiation of the hypoxic ventilatory response, and the optimum dose of domperidone required to reduce the suppressive effects of subanaesthetic doses of volatile agents on this response.

Subjects and methods

We studied 12 healthy male volunteers. The nature and purpose of the study were explained and written consent was obtained. The study was approved by the Local Ethics Committee. None of the subjects was receiving any medication throughout the study and all were asked to refrain from substances known to affect respiration (e.g. alcohol, tobacco, etc.) for at least 6 h before study.

Each subject attended the laboratory on five occasions. The first visit was a familiarization period where the ventilatory response to isocapnic hypoxia (oxygen saturation was reduced to 80% for 10 min) was measured. In the remaining four visits to the laboratory, subjects were allocated randomly to receive placebo or domperidone tablets 10 mg, 20 mg or 30 mg every 8 h for 48 h before and on the day of their visit to the laboratory. As this was a double-blind study, the number of tablets taken was standardized to three 8-hourly, regardless of dose of domperidone. To avoid any drug carryover effect, a washout period of at least 3 days separated treatment regimens for the same subject as the elimination half-life of domperidone is 12–16 h.[13] To minimize the effect of diurnal variation on the hypoxic ventilatory response,[14] subjects were scheduled to visit the laboratory at the same time of day for all four visits.

At each visit, subjects were asked about side effects while taking the tablets and were withdrawn from the study if they reported unpleasant adverse effects. We did not enquire about specific side effects. At the end of each visit, a venous sample was obtained for

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measurement of plasma concentrations of domperidone. The sample was separated by centrifugation and the resultant serum stored at –20°C. Samples were batched and sent to the Janssen Research Foundation in Belgium at completion of the study for measurement of plasma concentrations of domperidone.

The methods used for recording ventilatory variables have been described previously.[15] Briefly, subjects were seated upright in a comfortable armchair in a well-lit room and breathed via a mouthpiece and noseclip arrangement through a low resistance two-way valve. A five-way valve (Hans-Rudolf Gatlin Valve series 2430) was connected to the inspiratory port of the two-way valve to allow changes in inspired gases without the subject's knowledge. Expiratory gas passed via a heated pneumotachograph (Fleisch No. 2) and the signal was integrated to give breath-by-breath tidal volume. Inspiratory and end-tidal oxygen ($P\text{I}_{O_2}$, $P\text{E}'_{O_2}$) and carbon dioxide ($P\text{I}_{CO_2}$, $P\text{E}'_{CO_2}$) partial pressures were measured at the lips via a mass spectrometer (VG Spectralab M). Pulse oximetry (Sp_{O_2}) (Ohmeda Biox 3700, set to fast averaging time of 2 s) and electrocardiogram (Hewlett-Packard 78351A) were measured continuously throughout the study.

Breath-by-breath values of inspiratory time ($T\text{I}$, s), expiratory time ($T\text{E}$, s), total breath time ($T\text{TOT}$= $T\text{I}$+$T\text{E}$, s), ventilatory frequency (f=60/$T\text{TOT}$, bpm), tidal volume ($V\text{T}$, litre BTPS), instantaneous minute ventilation ($\dot{V}\text{E}^{inst}$=f×$V\text{T}$, litre BTPS), mean inspiratory flow ($V\text{T}$:$T\text{I}$, litre s^{-1}), inspiratory time:total breath time ratio ($T\text{I}$:$T\text{TOT}$), Sp_{O_2} (%), inspired and end-tidal partial pressures were digitized using a DEC PDP 11/23 computer and stored on disk for off-line analysis. During each study, subjects listened to music through headphones to mask any laboratory noise and were requested to remain awake. The laboratory was well-lit to help prevent subjects falling asleep.

Subjects breathed room air for 15 min before two breaths of 100% nitrogen were given followed by an inspired oxygen concentration of 10% to reduce oxygen saturation abruptly to 80–82%. This was maintained for 10 min after which one breath of 100% oxygen was given before returning to room air and the study terminated. Isocapnia was maintained during the 10 min hypoxic period by addition of carbon dioxide to the inspired gas.

DATA ANALYSIS AND STATISTICS

The relationship between domperidone dose and plasma domperidone concentrations for the group was determined and subjected to the Friedman test and Dunn's multiple comparison test for significant differences.

Mean values of the measured ventilatory variables were calculated for each subject for every minute of each study. Two specific 1-min periods were used for analysis based on minute ventilation. They were: baseline ventilation during normoxia (B), defined as minute ventilation during the last minute before the onset of hypoxia, and peak minute ventilation during the hypoxic period (H) (fig. 1). The acute hypoxic ventilatory response was defined as the difference between the two periods H and B. The Friedman test was used to examine the effect of increasing domperidone dose on baseline ventilation (B) and the hypoxic response (H–B). In cases of statistical significance, multiple pairwise comparisons were made *post hoc* with Dunn's multiple comparison test.

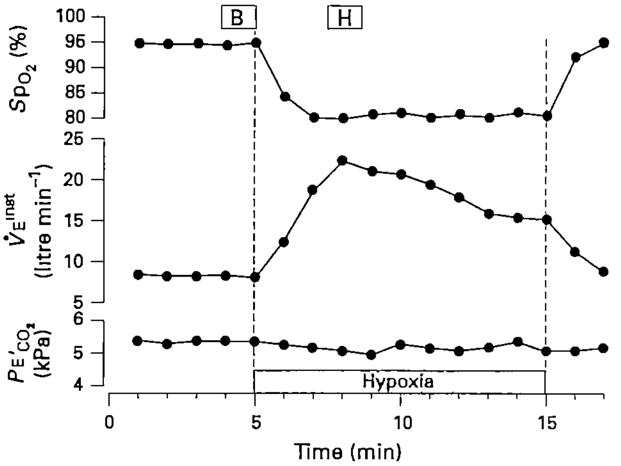

Figure 1 Oxygen saturation (Sp_{O_2}), instantaneous minute ventilation ($\dot{V}\text{E}^{inst}$) and end-tidal carbon dioxide ($P\text{E}'_{CO_2}$) plotted against time, for a typical subject. Mean values for each 1-min period are presented, with periods B (baseline ventilation) and H (peak ventilation during hypoxic period) shown for this subject.

As the bioavailability of oral domperidone is low (approximately 13–17%[16]) because of hepatic and gut wall metabolism, plasma domperidone concentrations for any of the dose regimens may vary substantially. To allow for this possibility, individual results of hypoxic responses were plotted against plasma domperidone concentrations and the best linear relationship fitted (using the least squares linear regression method) for every subject. Further analyses were undertaken using parametric or nonparametric tests as appropriate.

To assess the quality of the imposed ventilatory variables (i.e. $P\text{E}'_{CO_2}$, Sp_{O_2} and $P\text{E}'_{O_2}$), two-way analysis of variance for repeated measures (balanced design) was performed. In cases of statistical significance, multiple pairwise comparisons were made *post hoc* with the Tukey test. Statistical significance was set at P<0.05 for all analyses. All computations were carried out using GraphPad Prism 2.01 statistical package, running within MS DOS 6.2.

Results

All 12 subjects completed the study visits without any complications and none reported significant side effects. Two of the 12 subjects had markedly irregular breathing which made analysis of ventilatory variables extremely difficult and they were excluded from analysis. The 10 subjects analysed had a mean age of 33 (range 26–49) yr, mean height 1.80 (1.64–1.88) m and mean weight 76.8 (60.0–94.5) kg.

With domperidone 10 mg, plasma concentrations were median 9.7 (interquartile range 7.5–14.4) ng ml^{-1}, which increased to 25.1 (22.6–28.9) ng ml^{-1} with 20 mg. Concentrations after 30 mg (30.3 (20.1–33.2) ng ml^{-1}) were not significantly different from those after 20 mg.

In all subjects, the abrupt reduction in oxygen saturation to 80% (±2%) caused a sharp increase in ventilation, with peak ventilation occurring within

Table 1 Mean (SD) imposed variables in the two measurement periods for the four treatment regimens. B=Baseline; H=hypoxia

			Domperidone					
	Placebo		10 mg		20 mg		30 mg	
Variable	B	H	B	H	B	H	B	H
$P_{E'_{CO_2}}$	5.29	5.26	5.30	5.30	5.33	5.32	5.28	5.31
(kPa)	(0.24)	(0.24)	(0.31)	(0.28)	(0.44)	(0.47)	(0.34)	(0.39)
$P_{E'_{O_2}}$	13.37	6.04	13.29	6.07	13.28	5.79	13.45	5.94
(kPa)	(0.46)	(0.36)	(0.43)	(0.24)	(0.60)	(0.30)	(0.47)	(0.38)
Sp_{O_2}	95.8	79 1	95.3	78.3	96.3	78 9	95.6	78.9
(%)	(1.8)	(1.8)	(1.6)	(1.1)	(1.2)	(1.1)	(1.3)	(1.4)

Table 2 Acute hypoxic ventilatory response for the four treatment regimens for all subjects

		Domperidone		
Subject No.	Placebo (litre min^{-1})	10 mg (litre min^{-1})	20 mg (litre min^{-1})	30 mg (litre min^{-1})
1	3.57	4.18	2 50	4.69
2	9.46	8 56	19.45	15.60
3	7.65	7.94	13.36	27.04
5	8.72	5.93	10.76	4.23
6	8.21	15.56	22.30	25.85
7	4.48	9.31	6.27	4.25
8	8.83	6.61	10.21	6 74
9	7.64	3.53	4.73	5.77
11	8.27	19.40	20.82	11.22
12	3.74	4.79	15.78	15.69
Median (interquartile range)	7.93 (6.06, 8.05)	7.28 (5.36, 8.94)	12.06 (8.24, 17.61)	8.98 (5.23, 15.65)

the first 5 min followed by a decline in ventilation by the end of the 10-min hypoxic period. Ventilation returned to baseline on returning to normoxia. There were no significant differences in $P_{E'_{CO_2}}$ during the measurement periods for all domperidone treatment regimens in all subjects. Sp_{O_2} during the hypoxic measurement period (H) was not significantly different for all domperidone doses for any of the subjects. This was also the case for $P_{E'_{O_2}}$. Table 1 shows the results for imposed ventilatory variables.

Increasing doses of domperidone did not significantly affect either baseline minute ventilation or mean inspiratory flow rate. The hypoxic responses for each subject for all four treatment regimens are shown in table 2. There was no significant difference in the hypoxic response between the four treatment regimens (Friedman test) but there was a trend for the 20-mg dose of domperidone to be greater than placebo. However, when individual subject hypoxic responses were plotted against plasma domperidone concentrations and linear relationships constructed, they appeared to fall into two groups: five subjects (subject Nos 2, 3, 6, 11 and 12) showed a good hypoxic response to increasing concentrations of domperidone (increase of at least 2 litre min^{-1} per 10 ng ml^{-1} increase in plasma domperidone concentration) and the other five only minimally (fig. 2). When the slopes of these two groups were compared using the Mann–Whitney *U* test, they differed significantly (P=0.008). No correlation was found between the magnitude of placebo hypoxic response and the responsiveness to increasing concentrations of domperidone (correlation coefficient=0.31).

In the group of subjects whose hypoxic responses were augmented by at least 2 litre min^{-1} per 10 ng ml^{-1} increase in plasma domperidone concentration (table 3), there were differences between treatment regimens (Friedman analysis, P=0.003). The hypoxic responses of domperidone 20 mg and 30 mg were

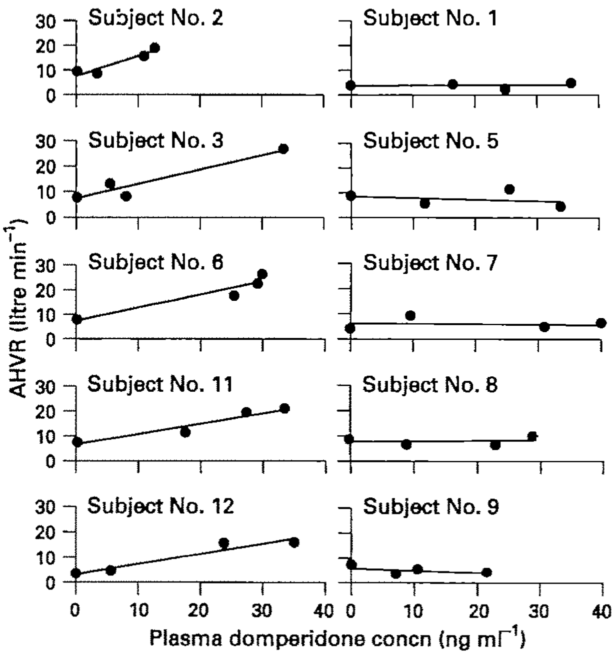

Figure 2 Individual subject hypoxic responses (acute hyoxic ventilatory response (AHVR)) plotted against plasma domperidone concentration with regression lines. Subject Nos 2, 3, 6, 11 and 12 on the left responded briskly to increasing concentrations of domperidone.

Table 3 Acute hypoxic ventilatory response for the subjects (n=5) who showed a good response to increasing doses of domperidone (litre min^{-1}). *Significant difference (P<0.05) compared with placebo

	Placebo	Domperidone		
		10 mg	20 mg	30 mg
Median	8.21	8.56	19.45*	15.70*
(range)	(3.74, 9.47)	(4.79, 19.40)	(13.37, 22.30)	(11.22, 27.04)

significantly greater than those for placebo (*post hoc* Dunn's multiple comparison test) but no difference in hypoxic responses were found between placebo and the 10-mg dose or between domperidone 20 mg and 30 mg.

Discussion

In this study, we wished to determine the relationship between incremental doses of domperidone and the potentiation of the acute hypoxic ventilatory response in male subjects. We found that increasing the dose of domperidone beyond 20 mg 8 hourly did not reliably increase plasma domperidone concentrations further and plasma domperidone concentrations in different subjects given the same dose were quite variable. Domperidone did not affect baseline ventilation and increasing doses appeared not to augment hypoxic responses in our subjects but there was marked individual variation in hypoxic responsiveness to domperidone. In subjects who were sensitive to increasing doses of domperidone, hypoxic responses appeared to be greatest with the 20-mg dose but this must be interpreted with caution because only five subjects were analysed. It was not possible to predict which subjects were likely to respond to domperidone.

As we encountered wide plasma variations in a previous study[12] and the bioavailability of oral domperidone is 13–17%[16] because of substantial hepatic and gut metabolism, we opted for a 2-day treatment regimen for the different doses to achieve steady-state plasma concentrations. The variability in plasma domperidone concentrations found at each dose in this study was likely to be caused by individual differences in "first-pass" metabolism. However, pharmacogenetic differences in domperidone metabolism could not be excluded although we could find no evidence to support this hypothesis. Drug carry-over effects were also unlikely to be responsible for the variability in plasma concentrations at each dose level as we had a minimum 3-day washout period (the majority had 5 days) between finishing and starting the next treatment regimen.

We were surprised that increasing doses of domperidone did not augment the mean hypoxic response in our subjects. Our previous study[12] and other investigators[2 10 11] have demonstrated an increase in the hypoxic response in humans after pretreatment with domperidone. When the hypoxic responses were plotted against plasma domperidone concentrations in each of our subjects, we found that they either responded well to increasing doses or were only minimally responsive to the effects of domperidone. The effect of domperidone on the hypoxic response appears to be variable in humans, and in our study we probably encountered an exaggerated division in responses thus resulting in our inability to demonstrate any augmentation of the hypoxic response with domperidone pretreatment. Nevertheless, using our arbitrary division based on subjects' hypoxic response–plasma domperidone concentration relationship, we decided to perform subgroup analysis in subjects sensitive to the effects of domperidone as there was sufficient evidence from other investigators[2 10 11] that domperidone augmented the hypoxic response.

Domperidone, regardless of the dose used, did not affect baseline ventilation. Similar results were found in our previous study[12] and also by other investigators.[2 10] However, Bascom and co-workers[11] found that domperidone significantly increased baseline ventilation (mean increase of 2 litre min^{-1} or 14% of control baseline). This difference may have resulted from different study conditions. In the study of Bascom and colleagues, subjects were studied under conditions of mild hypercapnia while our study was conducted at isocapnia with subjects remaining at their resting $P\text{E}'_{CO_2}$ level throughout the hypoxic period. Both Javaheri and Guerra[2] and Delpierre and co-workers[10] used a rebreathing isocapnic hypoxic ventilatory response technique (maintaining end-tidal carbon dioxide concentration at 7%). Therefore, it was likely that different experimental conditions determined whether or not domperidone increased baseline ventilation.

Previous studies examining the influence of domperidone on the hypoxic response also showed wide variability in individual sensitivities. Delpierre and co-workers[10] gave domperidone 0.1 mg kg^{-1} i.v. and measured the ventilatory response to hypoxia 30 min after injection. They found a mean increase in the relationship of ventilation to Sa_{O_2} (slope A) of 50 (SD 64)% with progressive hypoxia (Sa_{O_2} 70–80%) after domperidone. The slope increased by more than 20% in only six of 10 subjects (their fig. 1). It is possible that they had also studied subjects who were minimally sensitive to the effects of domperidone, as found in our study. As their study used an i.v. preparation of domperidone, it was unlikely that the lack of effect seen in four of their subjects was a result of inadequate plasma concentrations. Unfortunately, plasma venous domperidone concentrations were not measured in their study. Similarly, Javaheri and Guerra[2] studied eight male subjects and found that domperidone 20 mg orally 8 hourly, significantly augmented the hypoxic response by a mean of 55%. However, by examining individual responses to domperidone (their fig. 2) it can be seen that at least three of their subjects responded only minimally to domperidone.

In contrast, Bascom and colleagues[11] examined six subjects and all had augmented hypoxic responses after domperidone pretreatment. As their subjects were studied under conditions of mild hypercapnia, this may well have influenced their overall results. Furthermore, Javaheri and Guerra[2] found that domperidone caused a small (but insignificant) augmentation of the hypercapnic ventilatory response. This small degree of potentiation of the hypercapnic ventilatory response coupled with the hypoxic/hypercapnic interaction at the peripheral chemoreceptors may well have resulted in all of Bascom's subjects increasing their hypoxic responses significantly after domperidone. Therefore, the available evidence suggests that subjects differ in their hypoxic sensitivity to domperidone and up to 50% of the population may not increase their hypoxic response when pretreated with domperidone. However, this may not be the case if hypercapnia was also present, as in Bascom's study. Further investigation would be required to assess the magnitude of the hypercapnic/hypoxic interaction after pretreatment with domperidone.

Our study attempted to examine the dose–response relationship between domperidone and the acute hypoxic ventilatory response. Only 50% of our subjects responded to increasing doses of domperidone and in this group we found the greatest increase with the 20-mg dose, with no additional effect from the 30-mg dose. However, as the number of subjects analysed was small, we were unable to assess if a plateau had been reached with the 20-mg dose without risking a type II statistical error. Nevertheless, 60 mg per day appears to be the maximal acceptable amount for most investigators using domperidone to treat gastrointestinal disorders.[9 17] Therefore, 20 mg 8 hourly would seem to be the most appropriate regimen for augmentation of the hypoxic response, although some variation in plasma domperidone concentrations achieved would be expected. Unfortunately, in our study, it was not possible to predict from baseline ventilatory variables which subject would be sensitive to domperidone.

Animal studies have suggested that there may be two sets of dopamine receptors (inhibitory and excitatory) located in the carotid body with different affinities for dopamine.[18] In a recent review of carotid body chemoreceptors, Gonzalez and co-workers[19] proposed that the more accessible dopamine receptors with higher affinity for dopamine were responsible for the inhibitory action of dopamine. Domperidone would be more likely to bind onto these high affinity inhibitory receptors rather than the low affinity dopamine excitatory receptors thus resulting in augmentation of the hypoxic response. The degree of accessibility of these high affinity inhibitory dopamine receptors to domperidone may account for the variation in hypoxic responses seen in humans or alternatively, differences in the expression of active transporters (e.g. P-glycoprotein) controlling the removal of domperidone from the carotid bodies may be responsible.[20]

In summary, we have demonstrated that domperidone increased the ventilatory response to hypoxia in only 50% of subjects. In those that were sensitive to the effects of domperidone, the 20-mg dose regimen appeared to be adequate in augmenting the hypoxic response. However, we were unable to predict which subjects would respond to increasing doses of domperidone.

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A physiology simulator: validation of its respiratory components and its ability to predict the patient's response to changes in mechanical ventilation

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Summary

We aimed to validate the mathematical validity and accuracy of the respiratory components of the Nottingham Physiology Simulator (NPS), a computer simulation of physiological models. Subsequently, we aimed to assess the accuracy of the NPS in predicting the effects of a change in mechanical ventilation on patient arterial blood-gas tensions. The NPS was supplied with the following measured or calculated values from patients receiving intensive therapy: pulmonary shunt and physiological deadspace fractions, oxygen consumption, respiratory quotient, cardiac output, inspired oxygen fraction, expired minute volume, haemoglobin concentration, temperature and arterial base excess. Values calculated by the NPS for arterial oxygen tension and saturation (Pa_{O_2} and Sa_{O_2}), mixed venous oxygen tension and saturation ($P\bar{v}_{O_2}$ and $S\bar{v}_{O_2}$), arterial and mixed venous carbon dioxide tension (Pa_{CO_2} and $P\bar{v}_{CO_2}$) and arterial pH were accurate compared with measured values. Subsequently, arterial gas responses to changes in minute volume or $F\text{I}_{O_2}$ were measured in 31 patients and were compared with the NPS prediction for each response. The 95% limits of agreement in predicting the magnitude of change were: arterial oxygen tension −2.07 to 2.47 kPa; Pa_{CO_2} −0.33 to 0.67 kPa; and pH −0.023 to 0.033. This investigation has validated respiratory components of the NPS. We recommend the NPS as a clinical tool for predicting the effects of alterations in mechanical ventilation in stable patients in the intensive care unit. (*Br. J. Anaesth.* 1998; **81**: 327–332)

Keywords. computers, simulation; model, physiological; ventilation, mechanical

Mathematical, pathophysiological models have been constructed previously[1–4] and have been demonstrated to be reasonably accurate and reliable.[1] The Nottingham Physiology Simulator (NPS) is a simulation of original, comprehensive cardiovascular, acid–base, respiratory, cerebrovascular and renal physiological models. The methods of modelling and of implementing the model as a computer simulation rely on intensive, repeated calculations and thus require significant computer power. The NPS, as an original simulation of original physiological models, requires validation.

Adjustment of inspired oxygen fraction ($F\text{I}_{O_2}$) and ventilatory minute volume ($\dot{V}$) in patients undergoing mechanical ventilation are performed frequently in the intensive therapy unit (ITU). The clinician's aim in performing these adjustments is attainment of optimal arterial oxygen and carbon dioxide partial pressures and plasma pH, while avoiding the deleterious effects of inaccurate ventilator programming, which include hypoxaemia, acidaemia, hypercapnia, pulmonary barotrauma[5–7] and pulmonary oxygen toxicity.[8 9] Prediction of the outcome of intervention in mechanical ventilation offers potential benefits. Computer models have been used previously to simplify such complex physiological scenarios.[10 11] We investigated the mathematical validity of the respiratory components of the model simulation and subsequently assessed the ability of the NPS to predict the patient's response to a change in ventilator settings.

Methods

THE NOTTINGHAM PHYSIOLOGY SIMULATOR

The NPS is a computer simulation of an original set of physiological models and is described in appendix 1 and figure 1.

EXPERIMENTAL METHODS (INITIAL INVESTIGATION OF MATHEMATICAL VALIDITY)

After obtaining approval from the Local Ethics Committee, we collected data from 25 patients receiving intensive therapy in the adult intensive care unit (AICU). Each patient had a pulmonary artery catheter and arterial cannula *in situ*. Patients had a variety of surgical and non-surgical pathologies and were not excluded on the basis of diagnosis. Thirty data sets were collected, each comprising the following values.

(1) Inspired oxygen fraction ($F\text{I}_{O_2}$) and expired minute volume were measured by the internal oxygen analyser and flowmeter of the Dräger Evita II ventilator. Each of these was calibrated before use in each patient.
(2) Arterial and mixed venous blood samples were

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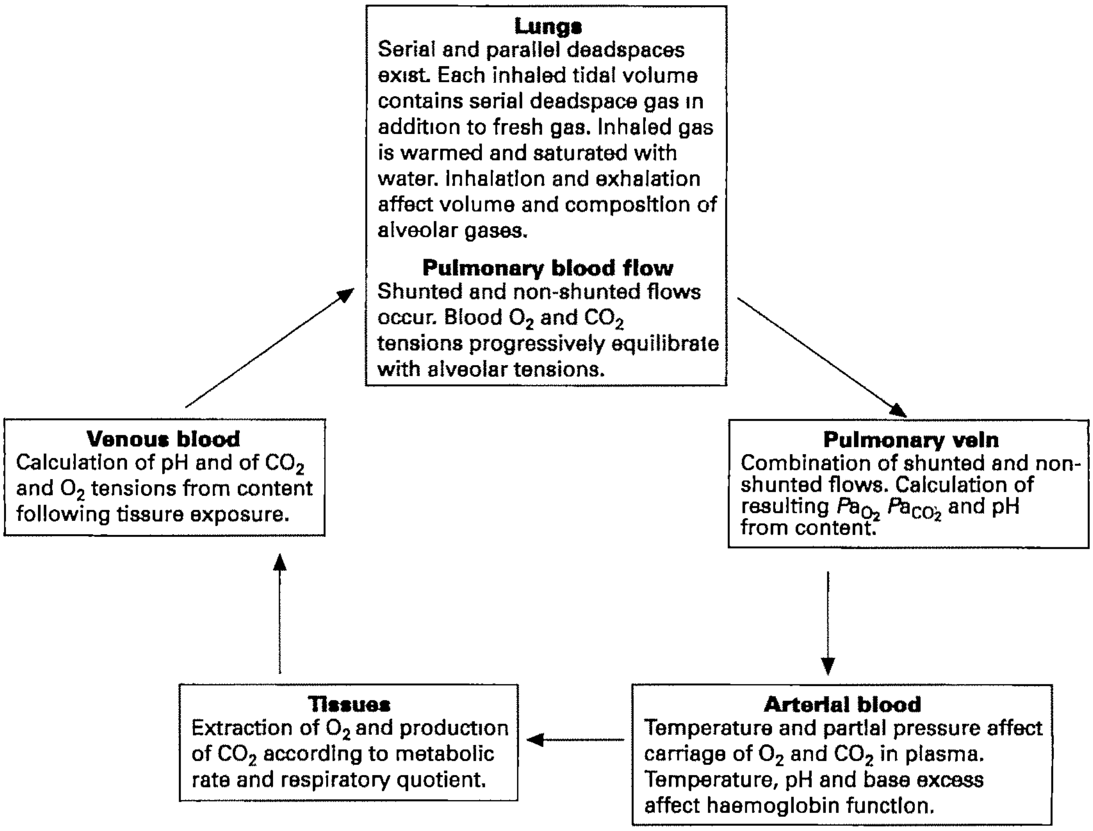

Lungs
Serial and parallel deadspaces exist. Each inhaled tidal volume contains serial deadspace gas in addition to fresh gas. Inhaled gas is warmed and saturated with water. Inhalation and exhalation affect volume and composition of alveolar gases.

Pulmonary blood flow
Shunted and non-shunted flows occur. Blood O_2 and CO_2 tensions progressively equilibrate with alveolar tensions.

Pulmonary vein
Combination of shunted and non-shunted flows. Calculation of resulting Pa_{O_2} Pa_{CO_2} and pH from content.

Arterial blood
Temperature and partial pressure affect carriage of O_2 and CO_2 in plasma. Temperature, pH and base excess affect haemoglobin function.

Tissues
Extraction of O_2 and production of CO_2 according to metabolic rate and respiratory quotient.

Venous blood
Calculation of pH and of CO_2 and O_2 tensions from content following tissure exposure.

Figure 1 Diagrammatic representation of some of the important features of the respiratory model of the Nottingham Physiology Simulator.

obtained simultaneously and analysed at 37°C for partial pressures of oxygen (Pa_{O_2}, $P\bar{v}_{O_2}$) and carbon dioxide (Pa_{CO_2}, $P\bar{v}_{CO_2}$), and pH, using a 278 blood-gas system (Ciba-Corning). It was calibrated with one- and two-point calibration cycles before use. Bicarbonate concentration, extracellular base excess (BE_{ecf}), temperature-corrected gas tensions and pH values were calculated manually (appendix 2), as details of the blood-gas analysis machine's algorithms were not available. Arterial and mixed venous oxyhaemoglobin saturations (Sa_{O_2}, $S\bar{v}_{O_2}$) were calculated using Thomas's equations.[12]

(3) Cardiac output was recorded and mixed venous and arterial blood were sampled simultaneously for gas analysis. A calibrated Edwards continuous cardiac output thermodilution Swan–Ganz catheter (Baxter Healthcare Corporation) interfaced to an Edwards critical care vigilance monitor (Baxter Healthcare Corporation) was used for measurement of cardiac output and core temperature.

(4) Peripheral venous haemoglobin concentration (Hb) was measured each morning. Patients whose haemoglobin concentration was likely to have changed significantly since it was measured (e.g. haemorrhage or haemodilution) were not recruited.

Pulmonary shunt fraction ($\dot{Q}_S:\dot{Q}_T$), metabolic oxygen consumption ($\dot{V}_{O_2}$), respiratory quotient (R), metabolic carbon dioxide production ($\dot{V}_{CO_2}$) and physiological deadspace fraction ($V_{D_{phys}}/V_T$) were calculated from each data set. Methods used to derive each are given in appendix 2. These calculated values were subsequently entered into the simulation in addition to the measured values of cardiac output, $F_{I_{O_2}}$, expired minute volume, Hb, temperature and arterial BE_{ecf}. The simulation calculated values for Pa_{O_2}, Sa_{O_2}, $P\bar{v}_{O_2}$, $S\bar{v}_{O_2}$, Pa_{CO_2}, $P\bar{v}_{CO_2}$ and arterial pH, and we compared these calculated values with those measured in our patients. Bias and 95% limits of agreement between measured and predicted values were calculated, as described below.

EXPERIMENTAL METHODS (PREDICTING THE PATIENT'S RESPONSE TO A CHANGE IN VENTILATOR SETTINGS)

After formal discussion with the Local Ethics Committee, it was felt that it was not necessary to obtain patient consent for the study as it was observational. Data were collected from 16 patients in the general intensive care unit who had been identified as requiring adjustment of mechanical ventilator settings. This patient group did not overlap with the group recruited to the preceding part of the study. Patients were not excluded on the basis of diagnosis. Those who demonstrated significant instability (i.e. mean arterial pressure could not be expected to remain within approximately ±10% over the equilibration period) were excluded as this instability could cause alterations in arterial blood-gas tensions unrelated to ventilator adjustments. Patients whose haemoglobin concentration was likely to have changed significantly since it was measured were not recruited. Those in whom the positive end-expiratory pressure (PEEP) was adjusted were excluded. Thirty-one data sets were collected from 16 patients undergoing mechanical ventilation. Each data set included arterial blood-gas analysis before and 10 min after a change in the settings of the mechanical ventilator. In addition, data sets included:

(i) Before intervention in ventilation: temperature measured using a calibrated, axillary skin probe, haemoglobin concentration, expired tidal volume, ventilatory frequency and $F\text{I}_{O_2}$, measured by the Dräger Evita II ventilator.
(ii) changes in the patient's ventilator settings, consisting of an adjustment of $F\text{I}_{O_2}$, ventilatory frequency, tidal volume or a combination of these.

The simulation was aligned with each patient's values measured before intervention (appendix 1a), generating an estimate of $\dot{Q}\text{S}:\dot{Q}\text{T}$, deadspace fraction and $\dot{V}_{O_2}$. For the purposes of alignment and in the absence of data obtained from invasive monitors, cardiac index was assumed to be 3 litre $\text{min}^{-1}\ \text{m}^{-2}$. The simulated "patient" was then subjected to the same change in ventilator settings. The resulting changes in $P\text{a}_{O_2}$, $P\text{a}_{CO_2}$ and arterial pH were recorded. Bias and 95% limits of agreement between predicted and measured magnitude of change were calculated as described below.

STATISTICAL METHODS

Calculation of bias in the prediction of resulting gas tensions and pH may not provide useful information as both increases and decreases in $F\text{I}_{O_2}$ and $\dot{V}$ are made, potentially reducing the apparent bias. For this reason, the "signless" magnitude of change was analysed. Bias was calculated as the mean of predicted minus measured magnitude of change. The 95% limits of agreement were calculated assuming a Gaussian distribution as bias±*k*×SD of (S–M), where S is the value predicted by the simulator and M is the measured value. The value of *k* is based on the *t* distribution with $k=2.04$ for the initial validation investigation ($n=30$) and for the size of the change in $P\text{a}_{O_2}$ ($n=31$), and $k=2.14$ for the size of the changes in $P\text{a}_{CO_2}$ and pH ($n=14$).[13] The correlation coefficient was calculated between the measured magnitude of change and the error in predicting the magnitude of change in $P\text{a}_{O_2}$, $P\text{a}_{CO_2}$ and pH in order to identify sources of error. Data processing, analysis, regression and charting were performed using Microsoft Excel (v. Excel 97).

Results

INITIAL INVESTIGATION OF MATHEMATICAL VALIDITY

Bias and 95% limits of agreement are given in table 1.

PREDICTING THE PATIENT'S RESPONSE TO A CHANGE IN VENTILATOR SETTINGS

All data sets included adjustment of $F\text{I}_{O_2}$ and 14 of the 31 data sets included alteration of $\dot{V}$ by changes in ventilatory frequency, tidal volume, or both. The mean magnitude of change in $F\text{I}_{O_2}$ was 0.153 (SD 0.055) and the mean magnitude of change in $\dot{V}$ was 1.38 (0.95) litre min^{-1}. Agreement between the predicted and measured size of the changes in $P\text{a}_{O_2}$, $P\text{a}_{CO_2}$ and pH were good (table 2, figs 2–4). However, bias was relatively large for the prediction of size of

Table 1 Comparison of measured output values and output values calculated by the model simulation. Mean values of the calculated output data are given. The 95% limits of agreement are presented as bias ±2.04×SD (S–M), where S is the simulator calculated value and M is the originally measured value, and bias = mean (S–M)

	Mean	Bias ±95% limits of agreement
$P\text{a}_{O_2}$ (kPa)	11.41	0.012±0.111
$S\text{a}_{O_2}$ (%)	94.8	0.02±0.14
$P\bar{\text{v}}_{O_2}$ (kPa)	5.42	0.001±0.020
$S\bar{\text{v}}_{O_2}$ (%)	67.5	–0 03±0 17
$P\text{a}_{CO_2}$ (kPa)	5.72	0 002±0.025
$P\bar{\text{v}}_{CO_2}$ (kPa)	6.33	0.003±0 026
pH_a	7.361	–0.0002±0.002

Table 2 Measured and predicted magnitude of change in $P\text{a}_{O_2}$, $P\text{a}_{CO_2}$ and pH following changes in ventilator settings $\text{LA}_{95\%}$ refers to 95% limits of agreement between measured and predicted values. All other data are given as mean (SD)

	Measured	Predicted	$\text{LA}_{95\%}$
$P\text{a}_{O_2}$ (kPa)	5 76 (3.25)	5.95 (3.51)	0.20±2.27
$P\text{a}_{CO_2}$ (kPa)	0 60 (0.45)	0.77 (0.55)	0.17±0.50
pH	0.040 (0.031)	0.044 (0.034)	0.005±0 028

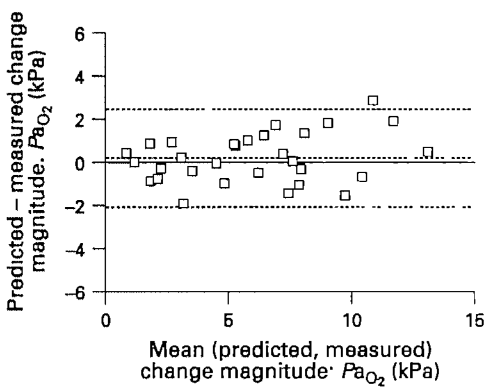

Figure 2 Errors in predicting the magnitude of changes in $P\text{a}_{O_2}$. The solid line represents absence of error, along which all points should, ideally, lie. The dotted lines represent the bias and 95% limits of agreement of predicted and measured values for magnitude of change in $P\text{a}_{O_2}$.

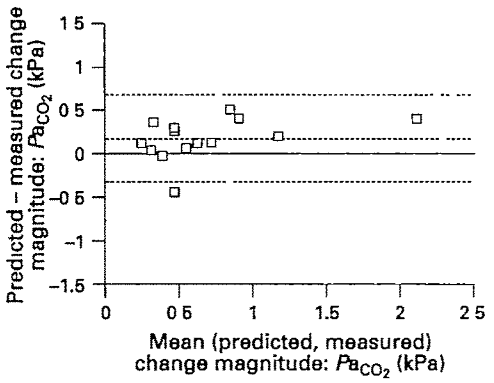

Figure 3 Errors in predicting the magnitude of changes in $P\text{a}_{CO_2}$. The solid line represents absence of error, along which all points should, ideally, lie. The dotted lines represent the bias and 95% limits of agreement of predicted and measured values for magnitude of change in $P\text{a}_{CO_2}$.

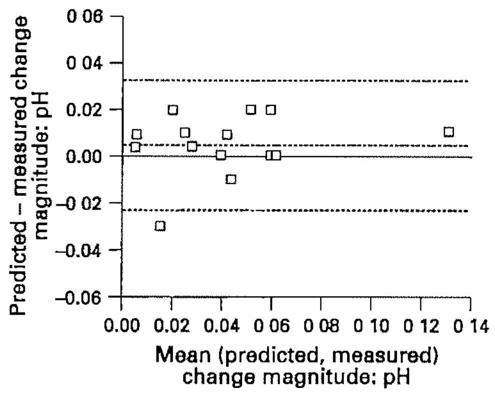

Figure 4 Errors in predicting the magnitude of changes in pH The solid line represents absence of error, along which all points should, ideally, lie. The dotted lines represent the bias and 95% limits of agreement of predicted and measured values for magnitude of change in pH.

change in Pa_{CO_2} after changes in ventilator settings, with an average overestimation of 0.17 kPa. A similar overestimation of the magnitude of the change in pH was observed. Correlations between measured size of change and error in predicting size of change for Pa_{O_2}, Pa_{CO_2} and pH (r=0.07, 0.17, −0.01, respectively) were weak and not statistically significant.

Discussion

INITIAL INVESTIGATION OF MATHEMATICAL VALIDITY

The close agreement of the re-calculated oxygen tensions (Pa_{O_2} and $P\bar{v}_{O_2}$) with oxygen tensions of the input data helps to validate several components of the respiratory model. These include the equilibrating alveolar and deadspace components, pulmonary perfusion component, oxygen carriage and transport components and the metabolic oxygen production component. The narrow limits of agreement for oxygen saturations (Sa_{O_2} and $S\bar{v}_{O_2}$) validate the NPS modelling of oxygen–haemoglobin interaction (incorporating Thomas' equations) in various conditions of pH, P_{CO_2} and BE_{ecf}. Accurate calculation of Pa_{CO_2} and $P\bar{v}_{CO_2}$ by the NPS validates the gas exchanging parts of the models, deadspace and shunt modelling, and temperature-dependent carbon dioxide solubility modelling. The agreement between measured arterial pH and that calculated by the NPS validates the NPS modelling of the Henderson–Hasselbalch relationship and base excess.

Inappropriate or unjustified modelling assumptions produce systematic errors, and minor problems in this area have not been excluded by this investigation. Significant programming errors usually produce marked errors with an observable pattern, and the existence of these seems unlikely in view of the results. The size of the errors observed suggests that they may be attributable to inadequate accuracy within either simulation of our respiratory models or in our calculation of values from patient data. The accuracy of the re-calculated physiological state is encouraging, providing validation of the mathematical consistency of the respiratory components of the simulation.

PREDICTING THE PATIENT'S RESPONSE TO A CHANGE IN VENTILATOR SETTINGS

The study group comprised patients from the intensive care unit. This group was chosen to provide a diverse set of data to validate the NPS. Adjustments of ventilator settings were of sufficient magnitude to allow validation of the NPS as a clinical tool.

Use of the iso-shunt concept, as described by Benatar, Hewlett and Nunn,[14] modification of the traditional shunt formula described by Hope and colleagues[15] or the PI_{O_2} *vs* Sp_{O_2} diagram[16] may provide reasonable estimations of $\dot{Q}S:\dot{Q}T$, assisting in the prediction of the patient's response to adjustment of FI_{O_2}. However, failure of iso-shunt lines to predict $\dot{Q}S:\dot{Q}T$ accurately does not necessarily cause inaccuracy in predicting the eventual Pa_{O_2} after intervention, as independent errors may cancel each other out. Thus the accurate solution by the NPS of $\dot{Q}S:\dot{Q}T$ or $\dot{V}_{O_2}$ may not be necessary for reasonably accurate prediction of Pa_{O_2} after intervention.

Errors may have been caused either by coincidental changes in patient physiological values during the equilibration period or by misalignment of the simulation to the patient. Errors may have come from invalid assumptions or programming errors in the simulation and this possibility may only be excluded by further validation of each section of the simulation. Figure 3 demonstrates a consistent prediction of too large a change in Pa_{CO_2}. It is possible that the 10-min interval between adjustment of ventilator settings and repeated sampling was inadequate. This interval was chosen as a compromise between three factors: (1) the longer the patient is left after adjustment of FI_{O_2} or $\dot{V}$ the more likely that physiological values alter unpredictably and coincidentally; (2) medical and nursing intervention can cause changes in the patient's state, unrelated to the recent change in ventilator settings. It was not feasible to stop interventions for long periods; (3) several minutes are required for equilibration to occur after alteration of FI_{O_2} and $\dot{V}$ and some workers have used longer periods.[17 18] Equilibration requires modification of dissolved tissue stores in addition to the gas reservoirs in blood and functional residual capacity.

A similar error was seen in the change in pH after intervention (fig. 4). This is likely to be caused by the error in the prediction of changes in Pa_{O_2} and may, in addition, represent the unpredictable variation of plasma base excess. Similar errors are not made in predicting changes in Pa_{O_2}, in agreement with other workers,[17] possibly because of the shorter interval required to reach equilibrium after a change in FI_{O_2}.

A comprehensive physiological simulation allows the introduction of a parallel "patient", with real-time manipulation of the model in the light of available patient data, constantly providing otherwise inaccessible data. The predictive power of such a parallel "patient" is limited only by the quantity and quality of data it receives and by the underlying physiological models. One cannot hope to achieve reliable estimation of cardiac output (for example) if the simulation is only "informed" of the patient's end-tidal carbon dioxide tension. The results suggest that provision of simple, relatively non-invasive data allows acceptable prediction of responses to a change in $\dot{V}$ and FI_{O_2}. One cannot validate an entire simulation of multiple complex processes simply. In this case, we have partially validated the respiratory model within the simulation, consisting of the lung, gas transport and tissue components.

The limits of agreement and bias between measured and predicted values after intervention imply a robustness and accuracy of prediction that allows the simulation to be recommended as a clinical tool. The systematic errors seen in predicting responses to changing $\dot{V}$ imply that this may be less accurate, especially if inadequate equilibration times are allowed after intervention. No method will achieve perfect prediction as there will always be physiological aspects of patients that may not be quantified and as physiological profiles may change coincidentally and unpredictably after an intervention.

In summary, we have confirmed the validity of the respiratory components of the NPS and we support its use as a reliable clinical tool.

Appendix 1

The Nottingham Physiology Simulator is a simulation of several original, physiological models. The respiratory model uses iterative refinement of physiological data sets to produce stable physiological scenarios and is made up of three major parts: pulmonary, transport and tissue compartments (see fig. 1). The lungs are modelled as comprising equipment, anatomical and alveolar deadspaces, and ventilated, perfused alveoli. Complete mixing of gases within the alveoli is assumed. Extraction of oxygen and excretion of carbon dioxide cause changes in lung volume and thus residual gas concentrations. Blood flow through the lung is modelled as two compartments: shunted and non-shunted blood.[1–3, 19] Blood flow past alveoli is "time-sliced" such that individual "packets" of blood are considered. Each packet comes to a true equilibrium with alveolar gases using an iterative process that includes the movement of gas between the alveolar and capillary compartments, generating an accurate simulation of the equilibration process.

Calculation of blood oxygen and carbon dioxide content after equilibration uses standard formulae and includes the effects of temperature, base excess and plasma pH.[12, 20, 21] Combination of pulmonary capillary blood with shunted mixed venous blood requires calculation of oxygen partial pressure from content. Thomas's equation is used iteratively to achieve this.[12, 21] Peripheral metabolism involves simple production of carbon dioxide and extraction of the preset $\dot{V}_{O_2}$. The resulting mixed venous gas contents depend on arterial gas content, $\dot{V}_{O_2}$, respiratory quotient and cardiac output. Base excess, temperature and plasma carbon dioxide content define plasma pH.

Appendix 1a

The model simulation is initially aligned to "hard data", including haemoglobin concentration, $F\text{I}_{O_2}$, core temperature, tidal volume, ventilatory frequency and plasma base excess. Subsequently, the alignment algorithm attempts to match the simulator values for $P\text{a}_{O_2}$ and $P\text{a}_{CO_2}$ with those of the patient. Metabolic consumption of oxygen (V_{O_2}), pulmonary shunt fraction ($Q\text{s}.\dot{Q}\text{T}$), respiratory quotient and alveolar deadspace fraction are adjusted, iteratively refining each variable, eventually producing a good fit of the simulation to the patient data. This single solution is not necessarily the correct or even the most likely solution. The simulator next calculates the probability density function of each variable given a set of predetermined confidence intervals, allocating it a probability of existing in isolation. The compound probability function is thus derived for the entire solution. The variables are then further adjusted to maximize the compound probability while maintaining a *possible* physiological solution for the data set. The simulator derives a viable solution to the physiological data (given the validity and internal consistency of the model) and maximizes the probability of its derived solution. However, in the absence of further data (e.g. cardiac output, end-tidal $P\text{co}_2$, $P\bar{\text{v}}_{O_2}$), it is not possible to make more confident predictions of the solution to each complex system.

Appendix 2

The following formulae were used in the calculation of physiological values from each data set. All pressures are measured in kPa and temperatures in °C.

HENDERSON–HASSELBALCH EQUATION[22]

$$\text{pH}=6.1+\log_{10}([\text{HCO}_3^-]/[\text{CO}_2])$$

where $[\text{HCO}_3^-]$=bicarbonate concentration; $[\text{CO}_2]$=carbon dioxide concentration, both measured in mmol litre^{-1}. $[\text{CO}_2]=0.2295\times P\text{a}_{CO_2}$ at 37°C.

CALCULATION OF BE_{ecf}[22]

$$\text{BE}_{\text{ecf}}=[\text{HCO}_3^-]-11.6\times(7.4-\text{pH})-24$$

where $[\text{HCO}_3^-]$=bicarbonate concentration calculated using the Henderson–Hasselbalch equation from pH and $P\text{co}_2$ at 37°C.

OXYGEN CONTENT

$$C\text{a}_{O_2}\ (\text{ml litre}^{-1})=\text{h}\times\text{Hb}\times S\text{a}_{O_2}+0.225\times P\text{a}_{O_2}/k$$

where h=oxygen carrying capacity of haemoglobin. The NPS uses a value for h of 1.36 ml g^{-1}, lying below the theoretical, maximal value of 1.39 ml g^{-1} (Hufner's constant), taking account of haemoglobin impurities such as methaemoglobin.[15] Hb=haemoglobin concentration (g litre^{-1}); $S\text{a}_{O_2}$=arterial oxyhaemoglobin saturation; $P\text{a}_{O_2}$=arterial oxygen tension; k=temperature correction for oxygen solubility, $k=1+\log(\text{temperature}/37)+0.00012\times(\text{temperature}-37)$.[2, 12]

CARBON DIOXIDE CONTENT IN BLOOD[23, 24]

$$C\text{a}_{CO_2}\ (\text{ml litre}^{-1}) = P\text{a}_{CO_2}\times 50.76/10^{0.019\times(\text{temperature}-37)}$$

RESPIRATORY QUOTIENT AND METABOLIC OXYGEN CONSUMPTION:

$$\text{R}=V_{CO_2}/V_{O_2}$$

$$\dot{V}_{O_2}=(C\text{a}_{O_2}-C\bar{\text{v}}_{O_2})/\text{CO}$$

where V_{CO_2}=metabolic production of carbon dioxide; V_{O_2}=metabolic production of oxygen; CO=cardiac output.

PULMONARY SHUNT FRACTION[25–27]

$$Q\text{s}:Q\text{T} = (C\text{c}'_{O_2}-C\text{a}_{O_2})/(C\text{c}'_{O_2}-C\bar{\text{v}}_{O_2})$$

where $C\text{c}'_{O_2}$ is estimated from alveolar oxygen tension:

$$P\text{A}_{O_2}\approx F\text{I}_{O_2}\times(P_\text{b}-\text{SVP}_{\text{H2O}})-(P\text{a}_{CO_2}/\text{R})+\{P\text{a}_{CO_2}\times F\text{I}_{O_2}\times(1-\text{R})/\text{R}\}$$

where P_b=barometric pressure (assumed to be 101.3 kPa); SVP_{H2O}=temperature adjusted saturated vapour pressure of water.

PHYSIOLOGICAL DEADSPACE FRACTION[26]

$$V\text{D}_{\text{phys}}/V\text{T}=1-(P_\text{b}\times\dot{V}_{CO_2})/(P\text{a}_{CO_2}\times\dot{V}_{\text{exp}})$$

where $\dot{V}_{\text{exp}}$=expired minute volume.

OXYHAEMOGLOBIN SATURATION[12, 28]

$$S\text{a}_{O_2}=(\text{n}^4-2\text{n}^3+36.33\text{n}^2+4.74\text{n})/(\text{n}^4-2\text{n}^3+42.64\text{n}^2-73.65\text{n}+757.5)$$

$$\text{n}=P\text{a}_{O_2}\times10^{\{0.48\times(\text{pH}-7.4)-0.024\times(\text{temperature}-37)-0.0013\times\text{BEecf}\}}$$

where BE_{ecf}=base excess of extracellular fluid.

TEMPERATURE CORRECTION OF PH[29, 30]

$$\text{pH}_T=\text{pH}_{37}-(T-37)\times(0.0147+0.00654\text{pH}_{37}-0.0484)$$

where pH_T=plasma pH at temperature T; pH_{37}=plasma pH at 37°C.

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Respiratory sinus arrhythmia and clinical signs of anaesthesia in children

C. M. BLUES AND C. J. D. POMFRETT

Summary

We have investigated changes in respiratory sinus arrhythmia (RSA) and compared these with clinical signs of anaesthesia in children. Children aged 3–10 yr were anaesthetized by gaseous induction with halothane and nitrous oxide. Multiple heart rate variability (HRV) spectra were obtained by power spectral analysis of continuous epochs of time from before introduction of halothane (baseline) until the pupils were central and fixed (stage 3). Measurement of RSA was performed by integration of the area under the spectral curve within the range of the respiratory frequency ± 0.15 Hz. In all patients RSA decreased continuously during induction unless stimulation occurred with insertion of an airway. Values of RSA were compared at three times: baseline, loss of pharyngeal tone and stage 3. The decrease in RSA from baseline to loss of pharyngeal tone and from loss of pharyngeal tone to stage 3 was significant (P=0.003 and P=0.018, respectively). These results show that RSA can be related to the clinical signs of anaesthesia and has potential as a measure of depth of anaesthesia in children. (*Br. J. Anaesth.* 1998; **81**: 333–337).

Keywords: heart, heart rate; measurement techniques, spectral analysis; anaesthesia, paediatrics; anaesthesia, depth

In health, heart rate varies constantly. These beat-to-beat changes in instantaneous heart rate are termed heart rate variability (HRV). Power spectral analysis has facilitated the study of the autonomic control systems that modulate HRV.

Two spectral components of HRV have been observed: a low frequency component mediated by both the parasympathetic and sympathetic systems and a high frequency component centred at the frequency of ventilation that is thought to be exclusively under parasympathetic control.[1–4] High frequency oscillation of heart rate with respiration is termed respiratory sinus arrhythmia (RSA) and is thought to be a selective index of vagal control of the heart[5] and a window on the autonomic activity processed in the nucleus solitarius of the brainstem.[6]

Since the suggestion that RSA may offer a method of measuring depth of anaesthesia,[7] several groups have studied the effects of general anaesthetic agents on RSA.[8–14] All of these studies measured RSA before and after induction of anaesthesia; the changes in RSA during the progressive stages of induction of anaesthesia have not been investigated.

The objectives of this study were to examine the changes in RSA during gaseous induction and to relate these changes to clinical signs during the progression through the stages of anaesthesia in children aged 3–10 yr. The higher spontaneous rate of respiration in this age group produces a distinct high frequency component that is needed for measurement of RSA.

Patients and methods

We studied 13 ASA I patients, aged 3–10 yr, undergoing elective ENT surgery. After approval of the local Ethics Committee, informed written consent was obtained from the parents. No patient had a history of autonomic dysfunction or was receiving any concurrent medication.

Children were premedicated with oral midazolam 0.5 mg kg^{-1}. On arrival in the anaesthetic room, monitoring leads were attached and the patient preoxygenated for as long as possible to provide a baseline measurement. Nitrous oxide was administered followed by as small increments of halothane as the clinical situation would permit until the pupils became small and central, and the eyes immobile (stage 3). The airway was secured as appropriate for the procedure and anaesthesia was maintained with oxygen, nitrous oxide and halothane.

Data were collected continually. Ventilatory flow was recorded using a Magtrak turbine (Ferraris Medical Ltd) inserted at the proximal end of the breathing system (T-piece). The Magtrak produced a flow-related pulse train during inspiration. Electrocardiogram (ECG) data were collected using standard ECG leads and recorded using a software controlled amplifier (CED 1902);12-bit digitized ECG and respiratory pulse trains were digitized at 1 kHz using a laboratory interface and commercial software (CED 1401 with Spike 2 software). From the parent and child's perspective, only routine monitors came into contact with the child; they were prepared for the presence of the computer in the anaesthetic room. End-tidal values of nitrous oxide, halothane and carbon dioxide were recorded together with MAC values, as calculated by a Datex Capnomac. The times of all events during induction were recorded using an event marker and the nature of the event was documented.

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Table 1 Values of heart rate (HR) and respiratory frequency (f) recorded at the three defined points during induction. Group values are shown as median (range). Statistical differences using the two-tailed Wilcoxon matched pairs signed ranks test: **$P<0.01$ compared with baseline; ††$P<0.01$ compared with loss of pharyngeal tone

	Baseline		Loss of pharyngeal tone		Stage 3	
Patient No.	HR (beat min^{-1})	f (bpm)	HR (beat min^{-1})	f (bpm)	HR (beat min^{-1})	f (bpm)
1	151	24	130	31	130	32
2	97	20	116	36	113	45
3	95	21	159	33	160	45
4	94	21	See text	See text	97	36
5	91	21	106	21	107	30
6	96	21	101	36	99	42
7	91	25	110	45	100	45
8	108	21	111	31	92	31
9	142	21	139	36	138	42
10	92	21	99	32	115	39
11	85	22	92	36	74	40
12	106	21	116	31	130	51
Median	95 (66)	21 (5)	111 (66)	33 (24)**	110 (86)	41 (21)**††

DATA ANALYSIS

Each R wave of the ECG was extracted from the data as an event using an algorithm for peak detection. Correct identification of every R wave was verified manually before analysis. A waveform was created by smoothing this event data over 1-s intervals using a raised cosine function and a sampling frequency of 4 Hz.[15] The result was a smoothed heart rate frequency curve (tachygram) representing equi-distant data suitable for spectral analysis. The same procedure was performed on inspiratory event times calculated from the Magtrak pulse trains, with a sampling frequency of 1 Hz. This gave an inspiratory tachygram with which to determine instantaneous inspiratory frequency. To remove slow trends in the data, a high-pass filter was applied to the re-sampled HRV tachygram series removing frequencies less than 0.056 Hz. A low-pass filter at 1 Hz was also applied to exclude components greater than the Nyquist frequency.[9]

Spectral analysis was then performed on 128-s segments of the filtered heart rate signal.[9 16] Starting at time 0, the analysis was repeated at 60-s intervals, thereby overlapping the epochs by 68 s. A 256-point fast Fourier transformation was applied to the data.

The power spectra describe HRV power as a function of frequency. HRV power within a frequency range was obtained by integration of the area under the power spectral curve. The spectrum was not normalized.[17 18–22]

Since the rate of spontaneous respiration varied, it was not appropriate to choose one band width for measurement of RSA. The high frequency component is centred around the frequency of respiration (f). The magnitude of RSA was thus measured as the power of the high frequency component of the variability spectrum that lay within the band width (f) ± 0.15 Hz.[19]

STATISTICAL ANALYSIS

No presumption of normality was made. RSA measured at three clinical stages was assessed using the two-tailed Wilcoxon matched pairs signed rank test. $P<0.05$ was considered statistically significant. The stages were: (1) before introduction of halothane (baseline); (2) loss of pharyngeal tone; and (3) return of the pupils to a central fixed position (stage 3). Loss of pharyngeal tone was taken as a stage as it was clearly identifiable without the need for stimulation of a reflex.

Results

One child was excluded because of a technical fault in data collection. We studied 12 children, aged 3–10 yr. A discernible high frequency peak corresponding to RSA was observed in all HRV spectra. The frequency of this peak increased as respiratory frequency increased during administration of halothane (table 1). There were no significant changes in heart rate.

The size of the RSA peak decreased markedly in all 12 children as they progressed through the stages of anaesthesia. The characteristic pattern of this decline is shown in figure 1, in which consecutive HRV spectra obtained from the overlapping epochs of time are shown for a single child (patient No. 3, table 2). Five epochs (1–3, 5, 6) have been taken from this plot and displayed sequentially in figure 2. Each HRV spectrum shows the RSA present at a specific clinical stage of anaesthesia. The HRV spectrum shown for the epoch at which stage 3 of anaesthesia is reached (fig. 2E) has been plotted on a magnified scale (x10).

A second complete plot, from patient No. 8, is shown in figure 3. In this plot a high level of low frequency activity can be seen. RSA increases initially as halothane is commenced and then decreases in the characteristic manner. The increase in RSA seen in epoch 6 corresponds to insertion of a Guedel airway.

This pattern of decline in RSA occurred in all 12 children. Despite this, grouping such continuous data for the purpose of statistical analysis is difficult as the speed of induction could not be standardized in the clinical situation. We took three clinical stages that were clearly identifiable in each of the children and compared the magnitude of the RSA (table 2). There was wide variation in absolute baseline values.

One patient was excluded from analysis of loss of pharyngeal tone as early insertion of an airway precluded its identification. In four patients, insertion of an airway unavoidably caused stimulation during the measurement period of stage 3 RSA (patient Nos 1,

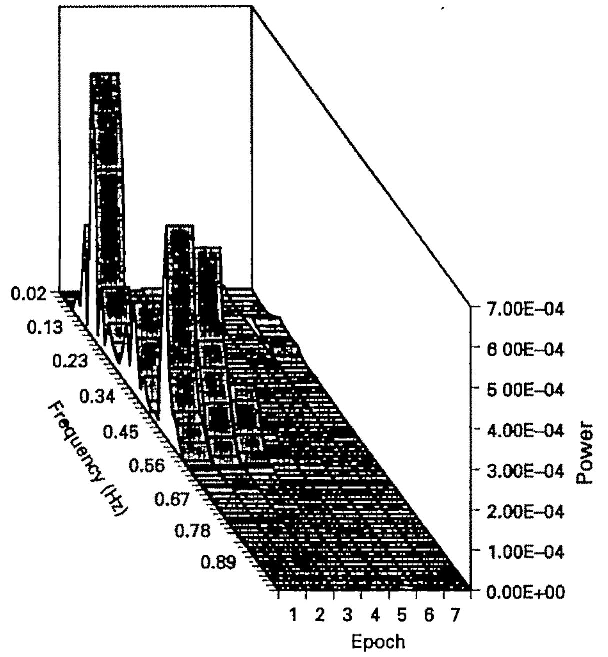

Figure 1 Three-dimensional plot of multiple heart rate variability (HRV) spectra obtained from consecutive overlapping epochs of time during induction of anaesthesia in patient No. 3.

2, 7 and 8) and therefore these patients are not included in the statistical analysis.

RSA decreased significantly between baseline measurement and loss of pharyngeal tone (P=0.003) and between loss of pharyngeal tone and stage 3 anaesthesia (P=0.018). When the values were considered as percentage change from baseline, the median value at loss of pharyngeal tone was 11.4% and at stage 3, 3.39%.

Discussion

We have demonstrated, for the first time, a continuous decrease in RSA during induction of anaesthesia, in the absence of stimulation, which can be related to the clinical signs of anaesthesia first described by Guedel in 1937.

The study of RSA in children confers an important methodological advantage. All quantitative measures of HRV are based on the premise of separable frequency ranges with no overlap. The high rate of respiration in children generates a high frequency component that can be separated clearly from the low frequency component.[3] In adults, this clarity can only be achieved by breathing in time to a metronome. By taking a band width for integration centred about the frequency of respiration of the monitored individual, we were able to minimize the loss of data falling outside the band width.

In 1935 it was first suggested that RSA may provide a quantitative measure for monitoring the level of anaesthesia when it was shown that RSA decreased in dogs after induction with ether[20] and halothane.[21] With the advent of microcomputers, interest in changes in RSA during anaesthesia was renewed. In 1985, Donchin, Feld and Porges, using measurement of R-R intervals, showed a decrease in RSA in 10 female patients after induction of anaesthesia with isoflurane.[7] Since then, several other studies have reported decreases in RSA after administration of anaesthetic agents.[8-14] Seven of these eight studies used i.v. induction of anaesthesia.[7 9-14] One study used gaseous induction with isoflurane but no measurements were made during induction.[8] Use of an i.v. induction agent precludes the study of RSA during induction of anaesthesia and introduces the problem of the effect of the induction agent itself on the autonomic nervous system.[22] Volatile agents also affect the autonomic nervous system, but the known cardiac properties of halothane would suggest a shift in the sympatho-vagal balance towards vagal predominance. Such an action would lead to an increase in the proportion of power within the high frequency band, the opposite effect to the decrease in RSA shown in this study. Seven of the studies compared pre-induction RSA in spontaneously breathing patients with RSA measured during controlled ventilation.[7 8 10-14] RSA is known to increase with controlled breathing despite no changes in variables of respiration or depth of anaesthesia.[4] All of these studies compared RSA measured before and at sometime after induction. Changes in RSA during induction of anaesthesia in spontaneously breathing patients have not been investigated previously.

The only studies of RSA in children have been in

Table 2 Values for respiratory sinus arrhythmia (% of baseline) measured at the three defined points during induction. Group values of absolute RSA and % of baseline are shown as median (range) and exclude epochs where stimulation occurred during the measurement period (labelled *). ** P<0.01 compared with baseline (n=11); †P<0.05 compared with baseline (n=8); ‡P<0.05 compared with loss of pharyngeal tone (n=7)

Patient No. (age in years)	Baseline RSA (% of baseline)	Loss of pharyngeal tone RSA (% of baseline)	Stage 3 RSA (% of baseline)
1 (5)	6.31E-06 (100)	1.01E-06 (16)	1.13E-06 (17)*
2 (5)	2.13E-04 (100)	5.78E-07 (0.3)	8.25E-07 (0.4)*
3 (5)	2.95E-05 (100)	3.40E-07 (1.1)	3.96E-08 (0.13)
4 (6)	9.13E-05 (100)	See text	3.48E-06 (3.8)
5 (7)	1.57E-04 (100)	1.45E-05 (9 2)	4.65E-06 (2.97)
6 (6)	3.79E-05 (100)	4.34E-06 (11.4)	1.50E-06 (3.94)
7 (5)	4.47E-04 (100)	3.84E-07 (0.08)	1.88E-06 (0.42)*
8 (4)	2.85E-05 (100)	3.42E-06 (12)	5.43E-06 (19)*
9 (3)	1.73E-06 (100)	7.76E-07 (44)	1.39E-07 (8)
10 (10)	8.93E-05 (100)	9.26E-06 (10)	2.78E-07 (0 3)
11(8)	3.13E-05 (100)	5.07E-06 (16)	4.42E-06 (14)
12(5)	5.7E-05 (100)	7.35E-06 (12.9)	1.9E-08 (0.03)
Median RSA	4.74E-05 (4.45E-04)	3.42E-06 (1.41E-05)**	8.9E-07 (4.63E-06)†‡
Median % baseline	100 (0)	11.4 (44.7)	3.39 (14)

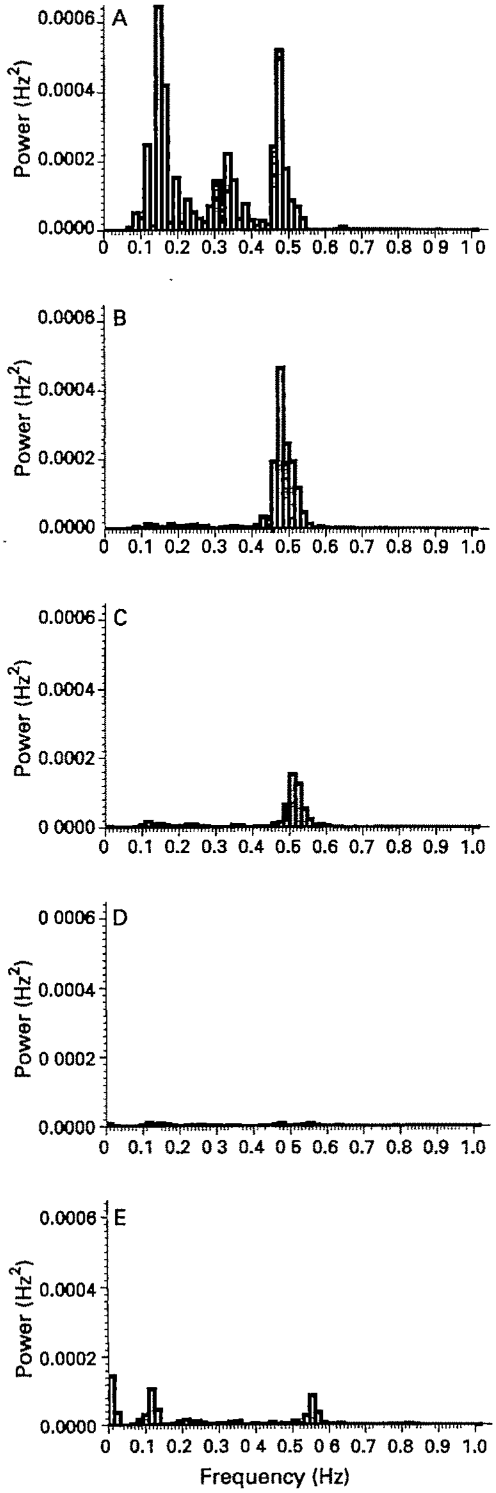

Figure 2 Heart rate variability (HRV) spectra during successive clinical stages of anaesthesia. A: Epoch 1, before introduction of halothane, respiratory frequency (f)=0.47 Hz. B: Epoch 2, after introduction of halothane during the excitement phase, f=0.47 Hz. C: Epoch 3, loss of eyelash reflex, f=0.51 Hz. D: Epoch 5, loss of pharyngeal reflex, f=0.56 Hz. E: Epoch 6, magnified view of RSA at stage 3, f=0.56 Hz.

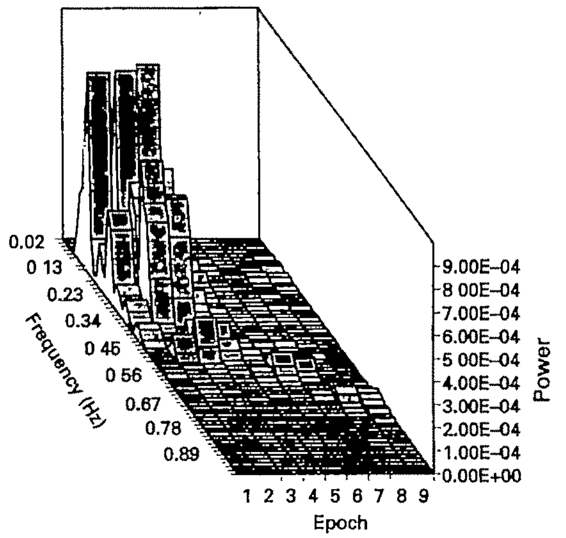

Figure 3 Three-dimensional plot of multiple heart rate variability (HRV) spectra obtained from consecutive overlapping epochs of time during induction of anaesthesia in patient No. 8.

neonates, investigating RSA as a tool for the differentiation of groups of neonates at risk from sudden infant death syndrome and in the assessment of neurological impairment after asphyxia.[24-27] RSA changes during anaesthesia in children have not been studied previously. Few studies have attempted to investigate any method of assessing anaesthetic adequacy in this age group. O'Kelly, Smith and Pilkinton examined the auditory evoked response but found the method unreliable because of the size of the patient and the consequent interaction between the signal frequency of the EEG and ECG.[23]

Studies in neonates demonstrate that this population can be divided into two distinct groups representing significantly different patterns for HRV.[19 28] One group has the majority of power concentrated in the high frequency range while in the second group, low frequency activity is dominant. Our study showed that the contribution of RSA to total power was also a variable feature in older children; some children had considerably more low frequency activity than others. This variation between children in the balance between sympathetic and parasympathetic control of the nervous system makes comparison of absolute values of RSA between individuals of little use in the study of the effects of anaesthesia. However, changes in RSA can be used to examine variations in vagal tone of an individual in different clinical situations. We followed each child through induction and compared the changes in RSA with baseline measurements. This was expressed as percentage change from baseline values.

When using RSA as an index of central vagal tone, it must always be remembered that this is a cardiac measure derived from the ECG. It reflects only the final vagal influences on heart rate. RSA represents not only the central levels of vagal activity that we wish to measure, but the working of the efferent pathways conducting the neural impulses, the traffic at the cholinergic receptor sites in the sinus node and the end organ itself, the heart.[29-31] When studying the effect of anaesthesia on brainstem autonomic activity, the effect of anaesthetic agents on the rest of the system cannot be ignored. We minimized this possible error by using only three agents (midazolam, halothane and nitrous oxide).

RSA offers considerable promise as a non-invasive and sensitive index of depth of anaesthesia in children. In five children a Guedel airway was inserted. In each case the stimulus was accompanied by an increase in power in the high frequency range and in the ratio of this component to the total power of the spectrum. In two patients, when an i.v. cannula was inserted after stage 3 had been reached, an increase in RSA was seen.

Future studies should investigate the relationship between changes in RSA and cognitive function using tests of cognition and memory. Such studies may need to be performed in an older age group. We have shown that RSA is a measure of the stage of anaesthetic depth in children but not as yet a measure of the level of conscious awareness.

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Changes in blood-gas tensions during apnoeic oxygenation in paediatric patients

T. M. COOK, A. R. WOLF AND A. J. W. HENDERSON

Summary

We report changes in arterial blood-gas tensions for up to 5 min of apnoeic oxygenation in 26 anaesthetized paediatric patients (21 children, five infants). Changes in oxygen and carbon dioxide tension were greatest in the first minute of apnoeic oxygenation. In subsequent minutes, rates of change in gas tension were approximately constant. The rate of decline in oxygen tension (31 (95% confidence interval (CI) 20.1–42.2) mm Hg min^{-1}) was more than three times that reported in studies in adults. The rate of increase in carbon dioxide tension (4.2 (95% CI 3.7–4.7) mm Hg min^{-1}) was similar to that reported in adults. After successful preoxygenation, oxygen tension remained greater than 290 mm Hg in all children (age >1 yr) throughout the study. This was not the case in infants. We found no correlation between changes in blood-gas tensions and age or weight of patients. The small number of infants studied showed rapid decreases in oxygen tension which if sustained would be expected to limit the safe duration of apnoeic oxygenation, unlike adults where apnoeic oxygenation is limited by hypercapnia. Extrapolation of our results suggests that when preoxygenation has been successful, apnoeic oxygenation could continue safely in children for at least 10 min. Infants may become hypoxic after only 2 min. (*Br. J. Anaesth.* 1998; **81**: 338–342).

Keywords: oxygen, saturation; oxygen, partial pressure; carbon dioxide, partial pressure; ventilation, apnoea; anaesthesia, paediatric

Apnoeic oxygenation is delivery of oxygen to an apnoeic patient and it is usually preceded by a period of preoxygenation so that maximal alveolar oxygen tension is achieved. Oxygen is then delivered to the patient with no effort to provide ventilation. Oxygenation depends on denitrogenation of the alveoli and airways so that oxygen uptake leads to mass transport of additional oxygen to the alveoli without nitrogen accumulation.

Apnoeic oxygenation is usually applied without attempts to increase airway pressure. However, apnoeic oxygenation may also be practised during continuous positive airway pressure (CPAP).[1] The delivery device may be in the pharynx[2] or trachea, and similar changes in gas tension occur.[2] In early apnoeic oxygenation studies, oxygen was not delivered to patients, instead they were connected to an oxygen-filled spirometer.[2]

In adults, oxygen flow rates of approximately 0.1 litre kg^{-1} min^{-1} provide adequate oxygenation during prolonged apnoeic oxygenation.[3] Apnoeic oxygenation of up to 55 min does not lead to hypoxaemia,[3] but severe hypercapnia and acidaemia develop as alveolar ventilation is negligible. Catecholamine concentrations increase and arrhythmias may occur.[3] The rate of increase of arterial carbon dioxide tension in adults is 3–4 mm Hg min^{-1}.[1 3] In the technique of endobronchial insufflation, oxygen is delivered via small bronchial catheters, rather than a tracheal tube, and arterial carbon dioxide tension may remain stable because of enhanced gas exchange.[4]

As neither arterial carbon dioxide tension nor pH are available routinely to the anaesthetist during surgery in an apnoeic patient, the safe time limit for apnoeic oxygenation is estimated. The above data suggest apnoeic oxygenation is safe in adults for at least 15 min.[2]

There are few data available on apnoeic oxygenation in paediatric patients. In particular we could find no data indicating safe limits for the technique in paediatric patients. Carbon dioxide tension may be expected to increase faster in paediatric patients because their metabolic rate is higher than that in adults relative to weight. However, apnoeic oxygenation via a paediatric tracheal tube may aid alveolar ventilation (similar to endobronchial insufflation in adults) because the small tracheal tube creates more airway turbulence and the distance from the carina to the alveolus is smaller. The relatively greater metabolic rate and potential for airway closure in paediatric patients may also result in a greater rate of decrease in oxygen tension and this could limit the safe duration of apnoeic oxygenation in this group.

Apnoeic oxygenation is an established practice in paediatric anaesthesia,[5] despite the absence of these data. We have examined the changes in blood gas variables during apnoeic oxygenation in paediatric patients. We related the effects of apnoeic oxygenation to age and weight.

Patients and methods

The study was approved by the local Research Ethics Committee. We studied 22 children (aged >1 yr) and

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Table 1 Patient details (median [range] or mean (SD))

Variable	
Age (months)	44 [1–142]
Weight (kg)	15.6 [3.7–48.6]
Haemoglobin (g dl^{-1})	10.8 (1.5)
Diagnosis (n)	
Patent ductus arteriosus	19
Minor coarctation of aorta	4
Mild pulmonary stenosis	2
Other	3

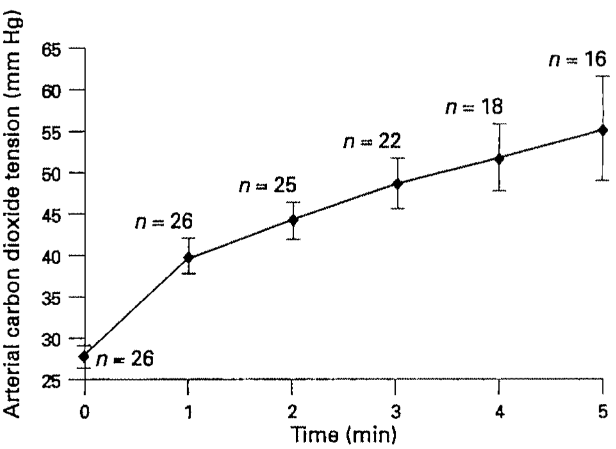

Figure 2 Changes in mean arterial carbon dioxide tension during the study. Error bars represent the outer limits of the 95% confidence interval.

six infants (age <1 yr), ASA I or II, undergoing cardiac catheterization, after obtaining written parental consent. Patients were excluded if they had significant cardiac shunt or abnormal cardiac performance, lung pathology or metabolic disturbance likely to alter metabolic rate, such as pyrexia or sepsis. Patients most suitable for this study were those undergoing mechanical closure of patent ductus arteriosus who were studied after duct closure.

Patients aged more than 4 months were premedicated 1 h before anaesthesia with diazepam 0.5 mg kg^{-1} orally and topical EMLA cream. Younger patients received EMLA cream only. In all cases cardiac catheterization was performed under general anaesthesia and intermittent positive pressure ventilation with standard anaesthetic monitoring, including capnography. Anaesthesia was induced with propofol 2–5 mg kg^{-1} and fentanyl 2 μg kg^{-1}. Intubation was preceded by pancuronium 0.1 mg kg^{-1} and an appropriately sized tracheal tube was passed to ventilate both lungs with minimal leak. The tip of the tracheal tube was positioned 2–3 cm beyond the vocal cords and confirmed radiographically. Anaesthesia was maintained with an infusion of propofol 8 mg kg^{-1} min^{-1}. Patients were draped with insulating materials to maintain body heat during the study. Fifteen minutes before the end of the procedure, atracurium 0.3 mg kg^{-1} was administered to maintain neuromuscular block. Ventilation was adjusted to achieve a stable end-expired carbon dioxide tension of 25 mm Hg. We anticipated that mild hyperventilation might lengthen the safe period of apnoeic oxygenation. The lungs were ventilated for 5 min with an $F_{I_{O_2}}$ of 1.0 before starting apnoeic oxygenation. During apnoea, oxygen was delivered to the anaesthetic system (Ayre's T-piece) at a rate of 1 litre min^{-1} throughout the period of apnoea (except where stated). The first arterial blood-gas sample was obtained at the same time as ventilation was stopped. Arterial blood samples were then obtained every 1 min for up to 5 min.

All blood-gas measurements were performed on blood obtained from a femoral artery cannula required for cardiac catheterization. After deadspace removal, 0.2 ml of blood was obtained for analysis. Measurement was performed immediately after sampling using a Ciba Corning 288 blood-gas analyser (Ciba Corning Diagnostics Corporation, Medfield, MA, USA).

The study was stopped if arterial carbon dioxide tension increased to greater than 70 mm Hg, pH decreased to less than 7.0, arterial oxygen tension decreased to less than 80 mm Hg or oxygen saturation decreased to less than 90%. The study was also stopped if the patient showed signs of respiratory effort, clinical desaturation or cardiovascular instability, such as ectopic beats, arrythmia or hypotension.

Statistical tests included Pearson correlation and regression analysis. The Wilcoxon–Mann–Whitney test was used for comparison between infant and non-infant groups. Tests were performed using Microsoft Excel 5.0 for Windows 3.1. $P<0.05$ was considered statistically significant.

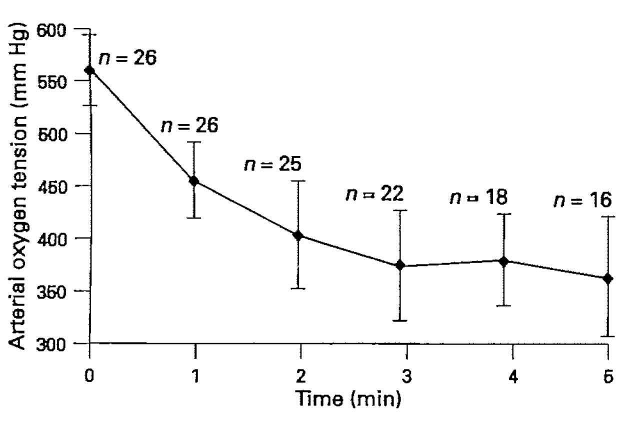

Figure 1 Changes in mean arterial oxygen tension during the study. Error bars represent the outer limits of the 95% confidence interval.

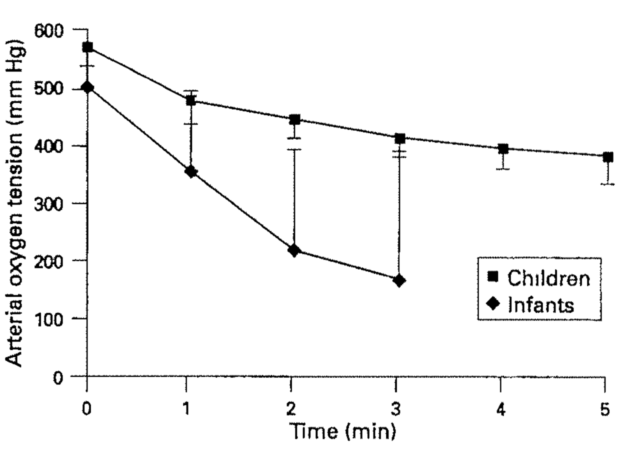

Figure 3 Mean oxygen tensions *vs* time for children and infants. Error bars represent the limits of the 95% confidence intervals

Table 2 Blood-gas tensions (mean (95% confidence intervals)

	t=0	t=1 min	t=5 min
$P\mathrm{o}_2$ (mm Hg)	561 (527–595)	456 (419–492)	366 (307–421)
Decrease in $P\mathrm{o}_2$ (mm Hg)		105 (84–125)	195 (150–238)
$P\mathrm{co}_2$ (mm Hg)	27.7 (26.5–29.0)	39.9 (37.9–42.1)	55.3 (49.1–61.5)
Increase in $P\mathrm{co}_2$ (mm Hg)		12.2 (10.5–13.9)	27.6 (21.5–32.6)
pH	7.48 (7.46–7.49)	7.38 (7.36–7.40)	7.29 (7.26–7.31)
Base excess (mmol litre^{-1})	0.78 (−1.6–0.1)	−0.8 (−1.5–0.0)	−2.2 (−3.2 to −1.1)

Table 3 Infants compared with children. Data are mean (95% confidence interval), unless stated.

	Infants	Children
n	5	21
Age (months) (median (range))	4 (1–7)	49 (15–142)
Weight (kg) (median (range))	6.5 (3.7–9.3)	20.1 (7.2–48.6)
Initial oxygen tension (mm Hg)	505 (384–625)	574 (539–609)
Decrease in oxygen tension in first minute (mm Hg)	148 (44–254)	95 (79–111)
Subsequent rate of decrease in oxygen tension (1–3 min)	60 (−10–129)	26 (21–31)
Initial carbon dioxide tension (mm Hg)	29 (24.5–33.4)	27.4 (25.9–28.9)
Increase in carbon dioxide tension in first minute (mm Hg)	14.9 (9.0–20.0)	11.6 (9.7–13.4)
Subsequent rate of increase in carbon dioxide tension (mm Hg)	3.7 (2.3–5.1)	4.3 (3.8–4.8)

Results

We studied 28 patients and one patient was studied twice. Patients were aged 1 month to 11 years 10 months; six patients were aged <1 yr (table 1). Two patients (one child and one infant) were excluded when initial blood-gas measurements showed that preoxygenation had been ineffective. Eleven patients were studied for less than 5 min: 10 began to breathe after 4 or 5 min, and in one infant oxygen tension decreased to 60 mm Hg after 3 min. There were no clinical sequelae to these events. No other patient was excluded because of clinical deterioration.

Mean oxygen tension decreased from 561 (95% confidence interval (CI) 527–595) mm Hg to 456 (95% CI 419–492) mm Hg at 1 min and 366 (95% CI 307–421) mm Hg at 5 min. Mean carbon dioxide tension at the start of apnoeic oxygenation was 27.7 (95% CI 26.5–29.0) mm Hg and increased to 39.9 (95% CI 37.9–42.1) mm Hg at 1 min and 55.3 (95% CI 49.1–61.5) mm Hg at 5 min. The changes in oxygen and carbon dioxide tensions with time are shown in figures 1–4. The greatest carbon dioxide tension recorded at 5 min was 80.4 mm Hg; the least pH was 7.16. Other data are summarized in table 2.

Oxygen tension decreased in all patients with the greatest decrease in the first minute in all but two patients. The mean initial decrease in oxygen tension was 105 (95% CI 84–125) mm Hg in the first minute and 31 (95% CI 20.1–42.2) mm Hg min^{-1} over the next 4 min (fig. 1).

The increase in carbon dioxide tension was greater in the first minute than in subsequent minutes in all patients. The mean increase in carbon dioxide tension was 12.2 (95% CI 10.5–13.9) mm Hg over the first minute and 4.2 (95% CI 3.7–4.7) mm Hg min^{-1} over the next 4 min (fig. 2).

One patient was studied on two occasions. On the first occasion oxygen was delivered at 1 litre min^{-1} and on the second occasion at 10 litre min^{-1} (equivalent to 0.03 and 0.3 litre kg^{-1} min^{-1}). Changes in oxygen and carbon dioxide tensions were remarkably similar in each study and were not suggestive of enhanced ventilation with the higher gas delivery.

Five infants (aged <1 yr) were studied. All weighed less than 10 kg. All four patients aged less than 6 months demonstrated rapid decreases in oxygen tension (fig. 3). One was withdrawn after 3 min because of low oxygen tension. Two did not complete 5 min of apnoeic oxygenation because they began to breathe. In one infant oxygen tension decreased from 487 to 115 mm Hg after 2 min of apnoeic oxygenation but decreased little in the next 3 min. The oldest infant, aged 7 months, weighing 9.3 kg, remained well oxygenated throughout 5 min of apnoeic oxygenation and the final oxygen tension was 351 mm Hg. Carbon dioxide tension increased at the same rate in infants as in children (14.9 mm Hg in the first minute, 3.7 mm Hg min^{-1} subsequently for infants; 11.6 mm Hg, 4.3 mm Hg min^{-1} for children) (table 3). There was no apparent difference in diagnosis between the five infants and 21 children.

Analysis of changes in oxyhaemoglobin saturation showed that it remained greater than 99% in all but two patients throughout the study. Mean saturation after 5 min of apnoeic oxygenation was 99.5%.

There was no significant correlation between changes in blood-gas tensions and patient age, weight or initial blood-gas tension.

Discussion

We have studied blood-gas tensions during apnoeic oxygenation via a tracheal tube in paediatric patients. By conducting the study during cardiac catheterization, we knew that cardiac shunt was not present.

Twenty-six of 28 patients achieved oxygen tensions greater than 370 mm Hg after preoxygenation. Two patients had initial oxygen tensions of less than 110 mm Hg. There was no clinical explanation for this, but gas leakage from a loose tracheal tube, atelectasis or a persisting shunt may have been responsible. We did not study these patients further and our results relate only to patients in whom preoxygenation was successful. Forty percent of patients did not remain apnoeic for the 5 min of the study and thus atracurium was not the ideal choice for neuromuscular block.

We used a fixed oxygen flow of 1 litre min^{-1} rather than varying flow with age or weight, as there is no published evidence that adequate gas flow in apnoeic oxygenation is related to weight or age, and airway geometry may be more relevant.

The only report on apnoeic oxygenation in children that we are aware of is an abstract published in 1987 by Kernisan and colleagues who studied apnoeic oxygenation in paediatric patients using oximetry. After preoxygenation, apnoeic oxygenation with oxygen flows of 0.1 litre kg^{-1} min^{-1} did not produce clinical desaturation in 3 min. Apnoea without tracheal oxygen led to desaturation in 217 s in heavy paediatric patients (>20 kg) and after 116 s in patients weighing <10 kg.[6] Our results confirm the safety of the technique in most patients: mean saturation after 5 min of apnoeic oxygenation was 99.5%. However, because two patients had low oxygen tensions after preoxygenation, and one infant became hypoxic after 3 min of apnoea, three of 28 patients were at risk of hypoxia.

We have produced a more thorough evaluation of the changes in blood-gas tensions during apnoeic oxygenation. As reported in adults,[1 2] the rates of decrease in oxygen tension and increase in carbon dioxide tension were greatest in the first minute of apnoeic oxygenation; changes in subsequent minutes continued but were reduced and largely constant. The early increase in carbon dioxide tension is caused by equilibration between alveolar and venous tension.[1]

Frumin, Epstein and Cohen[3] exposed eight adults to apnoeic oxygenation for up to 55 min; all patients remained well oxygenated with haemoglobin saturations in excess of 97%. After 30 min, pH decreased to less than 7.0 and carbon dioxide tension increased to 160 mm Hg. Arrhythmias were noted in two patients. Fraoli, Sheffer and Steffenson[2] exposed adults to 15 min of apnoeic oxygenation. Oxygen tension decreased from 445 to 310 mm Hg, carbon dioxide tension increased from 25 to 73 mm Hg and pH decreased from 7.55 to 7.20. The rate of decrease in oxygen tension in adults (9 mm Hg min^{-1}) was less than one-third of our value (31 mm Hg min^{-1}). The rate of increase in carbon dioxide tension in adults and paediatric patients was similar (3.2–3.8 mm Hg min^{-1} for adults, 4.2 mm Hg min^{-1} for paediatric patients). The reduction in pH in adults represents an increase in H^+ ion of 224% in 15 min. In this study, H^+ ion concentration increased 166% in 5 min.

The difference between adults and paediatric patients in the rate of decrease in oxygen tension is not surprising. Paediatric patients have a higher metabolic rate in relation to weight. As a result, the oxygen reserve in the lungs (functional residual capacity) is exhausted more rapidly.

The rate of increase in carbon dioxide in paediatric patients was less than we expected and was six-fold less than the decrease in oxygen. It is widely believed that paediatric patients have a relatively higher metabolic rate and a reduced storage capacity for carbon dioxide compared with adults and this led us to expect carbon dioxide tension to increase faster than in adults. A literature search back to 1966 found no data to support a reduced carbon dioxide storage capacity. Several methodological factors may have affected our results. The study was preceded by 5 min of preoxygenation and mild hyperventilation. Eger and Severinghaus found that the rate of increase in carbon dioxide tension in adults was reduced by approximately one-third when apnoea was preceded by hyperventilation to an initial carbon dioxide tension of 14 mm Hg.[1] We may have depleted tissue and blood carbon dioxide stores, so that storage capacity for carbon dioxide may have been artificially increased. Alternative explanations such as a significant decrease in cardiac output, regional blood flow distribution to metabolically inactive areas, or a decrease in metabolic rate are unlikely with mild hyperventilation, particularly as cardiac output and metabolic rate are higher in paediatric patients than in adults. A final possibility is that apnoeic oxygenation is providing some form of constant flow ventilation.

Endobronchial insufflation of oxygen or air in animal[7 8] and adult studies[4 9] permits adequate gas exchange for periods well in excess of 1 h. Gas exchange relies on bidirectional streaming and turbulent diffusion in the larger airways. In the distal airway, gas transport may be aided by oscillations caused by transmission of cardiac contractions,[10] but this is controversial.[4] For this effect, catheters must be placed 2.0–3.5 cm beyond the carina[11] and catheters with internal diameters less than 2 mm are needed to create sufficient turbulence. Gas flows need to be large; up to 1 litre kg^{-1} min^{-1} has been used in animals and flows in excess of 0.3 litre kg^{-1} min^{-1} are generally required to maintain blood-gas stability,[12] although airway geometry may be more important than weight in determining necessary flows. In our study, all tubes were placed above the carina, had internal diameters in excess of 3.5 mm and gas flows did not exceed 0.26 litre kg^{-1} min^{-1}, making the possibility of significant continuous flow ventilation extremely unlikely. When gas flow was increased 10-fold in one patient (to 0.3 litre kg^{-1} min^{-1}), carbon dioxide accumulation was unchanged, which supports this contention.

What clinical relevance can be inferred from our data? Oxygen tension remained greater than 290 mm Hg after 5 min of apnoeic oxygenation in all patients aged >1 yr. After the first minute, oxygen tension decreased by approximately 31 mm Hg min^{-1}. If this was sustained, hypoxia would be expected to develop after approximately 14 min of apnoeic oxygenation. Using the upper limit of our confidence interval (42 mm Hg min^{-1}), we could tentatively predict the development of hypoxia at 10 min. After 5 min of apnoeic oxygenation, carbon dioxide tension was less than 60 mm Hg in all but two patients. After the first minute, carbon dioxide tension increased by 4.2 mm Hg min^{-1} (upper limit of confidence interval 4.7 mm Hg). After 14 min of apnoeic oxygenation, carbon dioxide tension might therefore have increased to approximately 100 mm Hg. Therefore, it is likely that hypercapnia (and subsequent decrease in pH) limits the safe period of apnoeic oxygenation at a similar time to the development of hypoxia. These results contrast with the situation in adults where hypercapnia develops well before hypoxia.

The study was not designed to compare apnoeic oxygenation in infants and children but the small number of infants behaved differently from the children. Of particular concern was the fact that initial oxygen tensions were less in infants than in children, and rapid decreases in oxygen tension were seen in four of five infants.

One patient aged 7 months, weighing 9.3 kg, remained well oxygenated throughout the 5 min of apnoeic oxygenation. Mean decreases in oxygen tension for infants <6 months were 156 and 160 mm Hg in the first and second minutes, respectively (for all infants 148 and 60 mm Hg) and these were considerably greater than those in older children (95 and 26 mm Hg). As we used a fixed oxygen flow rate for all patients, infants had a higher oxygen flow relative to their size. Carbon dioxide tension increased in infants at the same rate as in children (14.9 mm Hg for the first minute, 3.7 mm Hg min^{-1} subsequently for infants; 11.6 mm Hg, 4.3 mm Hg min^{-1} in children). The large chest wall compliance of infants results in functional residual capacity being less than closing volume leading to the potential for airway collapse towards the end of expiration.[13] Awake infants can prevent airway collapse by partial closure of the glottis thereby "braking expiration".[14] In this study, paralysis and intubation would prevent this glottic braking, and subsequent airway closure may account for the rapid decrease in oxygen tension in infants. The clinical importance of these results is that hypoxia may occur in infants after 2 min of apnoeic oxygenation. Although the number of infants we studied was small, hypoxia occurred before clinically important hypercapnia. Therefore, the limiting factor for the safe duration of apnoeic oxygenation appears to be hypoxia in these patients. Oximetry is therefore mandatory to guide the safe duration of apnoeic oxygenation in infants.

On the basis of our results, we confirm that apnoeic oxygenation is safe for 5 min in most children and we would speculate that the upper limit of safe apnoeic oxygenation in children could be at least 10 min. Our results suggest that hypoxia may develop rapidly in infants.

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β_2-adrenergic responsiveness *in vivo* during abdominal surgery

C.-A. EWALDSSON AND R. G. HAHN

Summary

We have studied adrenergic function *in vivo* during anaesthesia and surgery. Epinephrine 50 ng kg^{-1} min^{-1} was given by i.v. infusion over 30 min to 10 healthy adult volunteers and to 10 patients undergoing abdominal operations. The cAMP response to stimulation by epinephrine, which was obtained as the area under the curve (AUC) for plasma cAMP concentration divided by the AUC for plasma concentration of epinephrine, was more pronounced during surgery (mean ratio 3.5) than in the control situation (ratio 1.4; $P<0.02$). This resulted in greater hypokalaemic and hyperglycaemic responses (ratios –0.67 and 4.5) than in the control group (ratios –0.33 and 1.6, respectively; $P<0.004$). Mean arterial pressure decreased in the control group while it increased in the study group, and serum cortisol concentration was higher in those who underwent surgery ($P<0.02$). These results are consistent with an increased adrenergic response during abdominal surgery. (*Br. J. Anaesth.* 1998; **81**: 343–347).

Keywords: surgery, abdominal; surgery, adrenergic response; blood, glucose, sympathetic nervous system, epinephrine; cardiovascular system, response; receptors, adrenergic

The adrenergic response, which is of paramount importance for physiological reactions during surgery, is dependent on the function of several molecular mechanisms.[1-4] The β-receptor operates by binding an agonist at the cell surface, which activates a specific G-protein which, in turn, catalyses the conversion of ATP to cyclic adenosine monophosphate (cAMP). This regulator of cell function alters the balance of phosphorylation that promotes specific adrenergic effects. Mechanisms for reducing the response include uncoupling of the β-receptor from the G-protein, increase in the distance between these molecular complexes (sequestration) and reduction in the number of receptors (down-regulation).[1 2]

Attenuation of the adrenergic response (desensitization) is known primarily to occur during adrenergic stimulation,[2 3] which is of interest as plasma concentrations of catecholamines (primarily epinephrine) become increased during surgery. Exhaustion has been confirmed *in vitro* by a reduction of the β-adrenergic receptor density on lymphocytes[4] and by reduced cAMP production on stimulation with isoproterenol,[5] while increased responsiveness has also been reported.[6] Fewer attempts have been made to measure β-adrenergic responsiveness *in vivo*.

In this study, we have looked for a set of variables based on blood chemistry and physiological reactions that are suitable for quantification of β-adrenergic responses during surgery. For this purpose, integrated time-effect profiles[7] were used to compare adrenergic agonist pressure with variables known to be affected by β_2-adrenergic receptor stimulation *in vivo* in a group of patients undergoing abdominal operations compared with a control group. Epinephrine was used as the adrenergic agonist as the purpose was to evaluate the sum of exogenous and endogenous β_2-stimulation. Serial measurements of the concentration of free cAMP in plasma were made as this variable indicates the level between receptor and effect at which any difference in adrenergic responsiveness is located.

Patients and methods

An i.v. infusion of epinephrine, dissolved in 500 ml of normal saline, was given at a rate of 50 ng kg^{-1} min^{-1} over 30 min (total dose approximately 0.1 mg) to 10 patients aged 34–56 (mean 45) yr undergoing abdominal surgery. The operations were colectomy ($n=2$), hysterectomy ($n=4$), resection of ovarian cysts ($n=3$) and pancreaticoduodenectomy (Whipple's operation, $n=1$). The same infusion was also given to 10 healthy volunteers (aged 31 (range 23–44) yr). All subjects were free from cardiovascular and pulmonary disease and were not receiving regular medications. The study was approved by the Ethics Committee of Huddinge University Hospital and all subjects gave informed consent.

All subjects were studied after fasting for at least 6 h. Premedication comprised morphine 7.5–10 mg i.m., approximately 1 h before arriving in the operating theatre. Anaesthesia was induced with thiopental and maintained with fentanyl 0.15–0.45 (mean 0.29) mg, and 1–3% isoflurane and oxygen in ambient air, as required. Oxygen saturation (pulse oximetry) and end-tidal carbon dioxide concentration were monitored continuously, the latter being maintained at 4.5–5.0 kPa. During surgery and the experiment, i.v. fluid supplementation comprised normal saline 4.0–7.0 (mean 4.9) ml kg^{-1} h^{-1}. Warm air blankets and warmed infusions were used to maintain body temperature within 37±1 °C, confirmed by

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oesophageal temperature monitoring in half of the patients.

The volunteers underwent the infusion experiment with epinephrine but received no other drug and did not undergo surgery.

Blood samples were obtained via a cannula placed in a cubital vein of the arm not used for infusion, immediately before the infusion started, and repeatedly over 100 min. In the surgical patients, the infusion was started immediately after skin incision. Specimens for measurement of plasma concentrations of epinephrine and cAMP were placed in ice water and centrifuged within 30 min. The remaining plasma was stored at −70 °C until analysed.

Plasma concentrations of adrenaline were measured by high pressure liquid chromatography.[8] Plasma concentrations of free cAMP were measured by ion-pair reversed-phase chromatography.[9] The free fraction is probably the most sensitive indicator of cAMP leakage from cells, although some of the cAMP also binds to plasma proteins. These analyses were performed with a coefficient of variation of 2%.

Blood glucose was measured using a colorimetric method (Johnson and Johnson Ektachem, Rochester, MI, USA), plasma cortisol by ELISA (Enzymun-Test, Boehringer Mannheim GmbH, Ingelheim, Germany) and plasma insulin by radioimmunoassay (Pharmacia RIA 100, Uppsala, Sweden). Serum potassium concentration was measured by a potentiometric test (Johnson and Johnson Ektachem). The coefficients of variation for these analyses were 4.6%, 5%, 6% and 4%, respectively. Confounding factors inherent in the sampling and analysis of serum potassium were avoided, including the use of a tourniquet, succinylcholine, muscle activity and haemolysis.

Heart rate and arterial pressure were measured every 5 min using a Datex AS 3 (Datex, Helsinki, Finland) or an HP 56S (Hewlett Packard Co., MA, USA). Mean arterial pressure (MAP) was calculated as the sum of diastolic pressure and one-third of the difference between systolic and diastolic pressures.

Glucose and insulin data from one volunteer were excluded because of suspected reduction of the cellular sensitivity to insulin. Her baseline insulin concentration was more than 10 times higher than the mean value for the other subjects.

Results are reported as mean (SD). When there was skewed distribution, median and range were used. Measurements that were performed frequently were also expressed as area under the curve (AUC) using the linear trapezoidal method. The half-life of epinephrine was estimated from the last three points in time using a monoexponential elimination function. Differences between treatments were evaluated by analysis of variance (ANOVA) or the Mann–Whitney test, as appropriate. Correlations were tested by simple and multiple linear regression analysis. Differences were reported to be significant at $P<0.05$.

Results

Infusion of epinephrine increased plasma concentrations of epinephrine, cAMP and glucose, and decreased serum potassium concentration (fig. 1). Changes over time for epinephrine, as measured by AUC, were slightly, but not significantly, higher in the control group than in those who underwent surgery (table 1). The reason became evident in our pharmacokinetic analysis, which showed that the terminal half-life of epinephrine was shorter during surgery (median 14 (range 6–28) min compared with 46 (17–122) min) (Mann–Whitney, $P<0.001$). However, cAMP and blood glucose responses to epinephrine were greater and serum potassium concentration tended to be more depressed in patients than in volunteers (table 1).

Change in serum potassium was the index of β-adrenergic stimulation that correlated most closely with AUC for plasma epinephrine (table 2; fig. 2, left). AUC for the decrease in serum potassium concentration also correlated with the magnitude of a further increase in plasma epinephrine concentration that occurred during the first 10 min after infusion ($r=-0.68$, $P<0.001$; fig. 1, upper left).

The ratios between AUC values were calculated to determine if any difference in β-adrenergic effect could be attributed to changes in the responsiveness to the first (epinephrine) or second (cAMP) messenger systems. This analysis showed that surgery was followed by significantly more pronounced changes in blood variables (cAMP, serum potassium and blood glucose) in response to infusion of epinephrine. In contrast, serum potassium and blood glucose responses to cAMP were the same in both groups (table 1).

As expected, heart rate increased when epinephrine was given. In contrast with all other indices of adrenergic response, the heart rate response to cAMP was greater in the control group than in the study group (table 3). MAP increased in the study

Table 1 Area under the curve (AUC) for changes in blood chemistry used as indices of β-adrenergic stimulation during and after i.v. infusion of epinephrine 50 ng kg^{-1} min^{-1} over 30 min in 10 volunteers (control group) and in 10 patients undergoing abdominal surgery. Data are mean (SD). P-Epinephrine=plasma concentration of epinephrine, P-cAMP = plasma concentration of cyclic AMP; S-K = serum potassium; B-glucose = blood glucose

	Control group	Abdominal surgery	ANOVA
AUC			
ΔP-epinephrine (nmol litre^{-1} min)	83.2 (27.4)	61.6 (33.1)	
ΔP-cAMP (nmol litre^{-1} min)	102 1 (36.5)	165 7 (51.4)	$P<0.005$
ΔS-K (mmol litre^{-1} min)	−26.7 (12.1)	−38.4 (19 5)	
ΔB-glucose (mmol litre^{-1} min)	112.1 (30.8)	215.1 (114.9)	$P<0.02$
AUC ratios			
ΔP-cAMP / ΔP-epinephrine	1.4 (1.0)	3.5 (2.3)	$P<0.02$
ΔS-K / ΔP-epinephrine (10^6)	−0.33 (0.12)	−0.67 (0.26)	$P<0.002$
ΔB-glucose / ΔP-epinephrine (10^6)	1.6 (0.9)	4.5 (2.7)	$P<0.004$
ΔS-K / ΔP-cAMP (10^6)	−0.29 (0.15)	−0.27 (0 19)	
ΔB-glucose / ΔP-cAMP (10^6)	1.3 (0.6)	1.4 (0.8)	

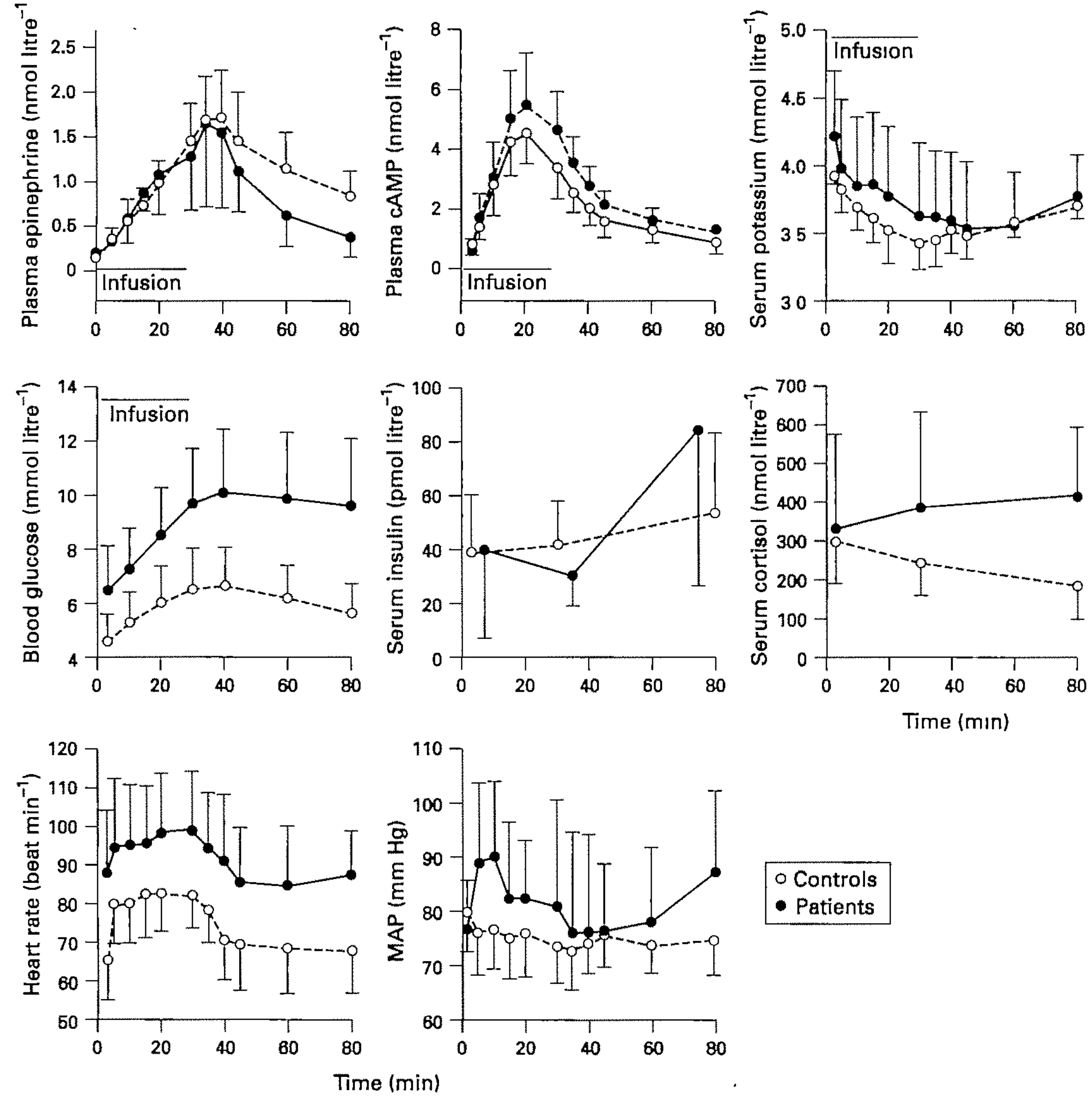

Figure 1 Concentration–time profiles of plasma concentrations of epinephrine, and cAMP, serum concentrations of potassium, insulin and cortisol, blood glucose, and heart rate and mean arterial pressure (MAP) during and after i.v. infusion of epinephrine 50 ng kg^{-1} min^{-1} over 30 min in 10 healthy volunteers (controls) and in 10 patients undergoing abdominal surgery (patients). Data are mean (SD).

group while it decreased in the controls, the latter being caused by a decrease in diastolic pressure. AUC ratios for MAP were always significantly different between the study group and controls because of the opposite direction of the pressure change. Therefore, when all volunteers and patients were evaluated together, those who showed an increase in MAP had a stronger hypokalaemic reaction (r=–0.51, P<0.02) but tended to have a less pronounced increase in heart rate (P=0.053).

Several variables indicated stress during surgery. Tachycardia was noted when the study started in addition to a progressive increase in serum cortisol concentration in these subjects (P<0.02 and P<0.002 compared with volunteers; ANOVA at 30 and 80 min, respectively) (fig. 1). A stronger hyperglycaemic response in patients also made the glucose–insulin relationship extend over a wider range in those who underwent surgery, despite the fact that volunteers received the same dose of epinephrine (fig. 2, right). Surgical incision increased arterial pressure, which was higher in these patients throughout the remainder of the study.

Discussion

The function of the β-adrenergic receptor is often assumed to be depressed during surgery because of the effects of anaesthesia and intrinsic preoperative and intraoperative adrenergic stimulation. Such conclusions are usually based on *in vitro* stimulation of cAMP production or on measurements of receptor density and binding sites on leucocytes.[4 5] Physiological variables reflecting adrenergic responsiveness in the whole organism have occasionally been used in volunteer experiments[10] but not during surgery.

In this study, we evaluated responsiveness *in vivo*, from relationships between blood chemistry and haemodynamic state during adrenergic stimulation. Cyclic AMP resulting from adrenergic activation leaks out from cells and, although some breakdown occurs, plasma concentrations of cAMP and epinephrine correlate well in volunteers[11] and during surgery.[12] Therefore, the cAMP response was used as evidence of desensitization of the β-adrenergic receptor complex, while attenuation of the effects of epinephrine on serum potassium, blood glucose and heart rate indicated block of either the first or second messenger.[13–15]

Table 2 Outcome of stepwise multiple regression analysis of the AUC for all physiological effect variables *vs* AUC for plasma epinephrine concentration (nmol litre^{-1} min) during the infusion experiments. The significant variables are shown. The study group was denoted as 1=volunteers, 2=patients *When both variables in the analysis are considered

	Coefficient	*t* value	*r*	*P*
Intercept	14588			
AUC for Δserum potassium (mmol litre^{-1} min)	−250	4.89	−0.54	<0.0001
Study group	−6725	3.98	−0.80*	<0.0009

Table 3 AUC for changes in haemodynamic indices of β-adrenergic stimulation during and after i.v infusion of epinephrine. Data are mean (range). Ratios are expressed in the same units as AUC for the variables included.

	Control group	Abdominal surgery	Mann–Whitney test
AUC			
ΔHeart rate (beat min^{-1})	833 (235, 1343)	401 (10, 1087)	
ΔMAP (beat min^{-1})	−294 (−744, −7)	331 (−844, 2032)	*P*<0.02
AUC ratios			
ΔHeart rate/ ΔP-epinephrine	10.3 (2.1, 13.4)	6.6 (0.1, 25.5)	
ΔMAP/ΔP-epinephrine	−4.7 (−13.7, −0.1)	3.9 (−18.1, 47.3)	*P*<0.04
ΔHeart rate/ΔP-cAMP	8.3 (1 9, 25.5)	2.5 (0.1, 5.9)	*P*<0.02
ΔMAP/ΔP-cAMP	−2.9 (−18.2, −0.1)	2.2 (−6.2, 33.2)	*P*<0 01

The choice of adrenergic agonist for β_2 activation was crucial. Epinephrine was considered more suitable than a β_2-selective agonist as increased release of epinephrine from endogenous sources is part of the "stress" response to surgery. The use of epinephrine allows reasonable comparisons to be made between β_2 agonist pressure (here represented by the AUC for epinephrine in plasma) and physiological responses. In contrast, the use of a β_2-selective agonist would require that our value for agonist pressure considered the AUC for *both* infused β_2-selective agonist and endogenous epinephrine, which is a speculative approach. Epinephrine is not the ideal agonist, however, as it stimulates both β_2 and α receptors. Therefore, the dose was adjusted to generate predominantly β_2 effects.[16 17]

The results suggest that the responsiveness of the β_2-adrenergic receptor is increased, rather than decreased, during the first 80 min of abdominal surgery. This conclusion is based on the fact that the cAMP response was stronger for any concentration–time profile of epinephrine when surgery was performed. AUC ratios also showed that the hypokalaemic and hyperglycaemic responses to epinephrine were stronger during surgery. These differences can be attributed to the increased cAMP effect, as AUC ratios showed that the hypokalaemic and hyperglycaemic responses relative to cAMP stimulation were similar in both groups.

The marked increase in heart rate in the control group was probably a result of reflex tachycardia associated with vasodilatation in skeletal muscle resulting from stimulation of β_2-receptors. This view is supported by simultaneous reduction of mean arterial pressure, which was caused by a decrease in diastolic pressure, and by the high heart rate/cAMP ratio. In patients who underwent surgery, however, noradrenergic and sympathetic mechanisms probably contributed to more widespread activation of α receptors, which increased arterial pressure. Therefore, the increase in heart rate became less pronounced. An α effect in the patient group was also evidenced by depression of serum insulin concentration during infusion[13] while the sharp increase at the end of the study probably represented adjustment to high blood glucose concentration.

It may also be important that heart rate was much higher at the start of surgery compared with baseline

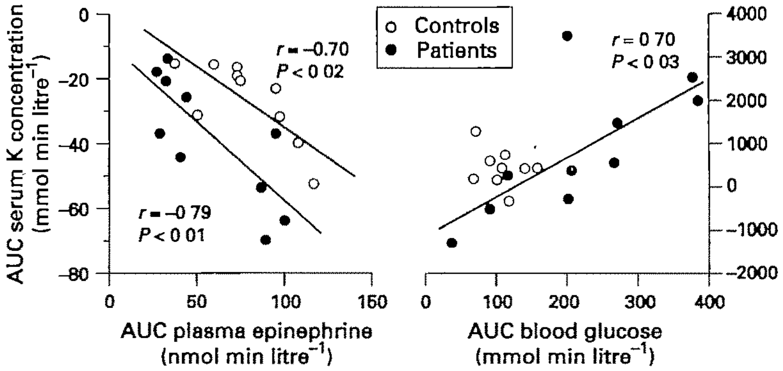

Figure 2 Area under the curve (AUC) for changes in the concentrations of serum potassium (K) and plasma epinephrine (left) and for blood glucose and serum insulin concentrations (right), during and after infusions of epinephrine. One datum point represents one experiment.

conditions in volunteers. One may assume that cAMP stimulation results in a greater increase in heart rate starting from a baseline pulse of 65 beat min^{-1} compared with 90 beat min^{-1}. The difference in heart rate can be regarded as the result of preoperative stress, which increases plasma epinephrine concentration,[19] and tracheal intubation, which is known to have the same effect.

Our data are consistent with an *in vitro* study by Tohmer and Cryer[6] who suggested that adrenergic responsiveness is increased 30–60 min after the onset of surgery while it is reduced after 4–6 h of surgery. Other *in vitro*[4 5] and *in vivo*[11] studies suggest that adrenergic responsiveness is reduced early during surgery. Löfgren and Hahn showed that absorption of epinephrine added to local anaesthetics used for intercostal nerve block immediately *after* open cholecystectomy was associated with the same responsiveness as in a control situation, despite the fact that plasma epinephrine concentrations were much higher in patients.[14]

Serum potassium concentration appeared to be the variable that correlated best with the degree of adrenergic stimulation, as indicated by the AUC for epinephrine in plasma. This finding is interesting as heart rate, vasodilatation and lipolysis (the latter a β_1 effect) are the most conventional physiological indices of β-stimulation *in vivo*.[10] Serum potassium concentration was measured after considering potential confounding factors, such as physical activity.[20] It does not matter much that baseline values differed slightly as only changes were used in the calculations. Epinephrine reduces serum potassium concentration by increasing the uptake of potassium in skeletal muscle via activation of Na–K-ATPase in cell membranes. The effect is mediated by β_2-receptors and is not obtained with isoproterenol, a catecholamine often used for studies of adrenergic responsiveness.[16]

Two factors should be considered when evaluating the results of our study. In both volunteers and patients, there was a paradoxical increase in epinephrine concentration in venous blood during the first 10 min after infusion of epinephrine was stopped. This "overshoot", which seems to be related to the degree of adrenergic effect as it correlated well with the hypokalaemic reaction, suggests that arterial blood sampling might have yielded higher values for plasma epinephrine during infusion of this catecholamine.

Second, the patients studied were generally older than the volunteers. But as β-adrenergic responsiveness decreases with age,[20] the difference in age between the groups cannot explain the increased responsiveness found. The shorter half-life of epinephrine in patients must also be a result of other factors—plasma clearance of epinephrine is known to decrease by approximately 20% in old age, and the epinephrine response to stress is reduced.[21] A more likely cause is increased peripheral uptake of the hormone as part of the "stress" response to surgery.

In summary, we have found that β_2-adrenergic responsiveness measured *in vivo* was increased slightly during the first 80 min of abdominal surgery. This does not preclude the fact that desensitization of β-receptors may occur in more prolonged operations.

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Effect of preoperative extradural bupivacaine and morphine on stump sensation in lower limb amputees

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Summary

We have examined the effect of preoperative extradural bupivacaine and morphine on postoperative stump sensation in 31 patients undergoing amputation of the lower limb in a prospective, randomized, double-blind study. Patients were allocated randomly to one of two groups: group 1 received extradural 0.25% bupivacaine 4–7 ml h^{-1} and morphine 0.16–0.28 ml h^{-1} before and during operation; group 2 received extradural saline before and during amputation and conventional analgesics for pain treatment. All patients received general anaesthesia for the amputation and extradural bupivacaine and morphine after operation. Sensory examination of the limb/stump was carried out before amputation, and after 1 week and 6 months. The following were measured: pressure pain thresholds (pressure algometry), touch and pain detection thresholds (von Frey hairs), thermal sensibility (thermal rolls), and allodynia and wind-up-like pain. There were no differences between the two groups at any of the postoperative assessments for mechanical and thermal sensibility or rate of allodynia and wind-up-like pain. Our study suggests that preoperative and intraoperative extradural block had no long-term prophylactic effect on hyperalgesia, allodynia or wind-up-like pain. (*Br. J. Anaesth.* 1998; **81**: 348–354).

Keywords: analgesic techniques, extradural; anaesthetics local, bupivacaine; analgesics opioid, morphine; surgery, amputation; pain, phantom limb

Pain after amputation is a significant problem among amputees. Approximately 60–70% of amputees suffer from phantom pain in the first year after amputation.[1 2] The mechanisms underlying pain in amputees are not clear but experimental and clinical evidence suggests that sensitization of central neurones before and during amputation may play a role.[3–6] Previous studies have shown that phantom pain is more likely to be present in amputees who had severe pain in the limb before amputation compared with those with less severe pain.[1 7 8] In a recent prospective study of 56 patients undergoing amputation, intense pain before amputation was associated with phantom pain in the first 6 months after amputation, and stump and phantom pain were significantly related 1 week after amputation.[2] Some studies have reported that phantom pains are similar to previously experienced pains in a high proportion of amputees[5 9] suggesting that pain experienced before amputation creates an imprint in pain memorizing structures in the central nervous system (CNS).[10] Taken together these findings suggest that long-term and intense noxious input from the periphery may induce changes in the CNS resulting in sensitization and chronic pain.

The manifestations of sensitization include, apart from pain, reduction in pain threshold (hyperalgesia), evocation of pain by non-noxious stimuli (allodynia) (for review see Willis[11]) and pain elicited by repeated pricking stimuli (wind-up-like pain).[12] Consistent with this are reports of abnormal stump sensibility in 50% of amputees[1] and descriptions of wind-up-like pain in amputees.[13]

Central sensitization after persistent noxious input raises the question of whether or not such neuronal hyperexcitability can be prevented. Several studies support the notion that signs of hyperexcitability after experimental nerve injury can be reduced by various treatments before or during injury.[14–16] A clinical correlate to such pre-emptive effects was the observation that preoperative extradural block prevented phantom pain.[17] However, not all studies support this finding. In a recent study, extradural bupivacaine and morphine administered for 18 h before, during and after amputation failed to reduce the rate and intensity of phantom pain in the first year after amputation.[18]

Previous clinical studies have suggested that it is possible to prevent signs of hyperexcitability other than pain by preoperative or intraoperative treatment.[19–21] For example, Richmond, Bromley and Woolf[19] found lower pain sensitivity around the wound in 15 patients who received morphine before hysterectomy compared with 12 patients who received morphine after operation.

While these studies suggest that intense treatment may reduce hyperexcitability in the early postoperative period, there is limited evidence for a reduction in long-term hyperexcitability. This is important because some surgical procedures, such as amputation, mastectomy and thoracotomy, are often associ-

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ated with long-term pain, allodynia, hyperalgesia and wind-up-like pain.[22-25] Therefore, we have examined, in a prospective, randomized, double-blind study, if extradural pain treatment started before amputation and continued into the postoperative period would reduce mechanical and thermal hyperalgesia, allodynia and wind-up-like pain 1 week and 6 months after amputation.

Patients and methods

Patients were recruited from 60 patients who took part in a major study of the effect of extradural bupivacaine and morphine in the prevention of stump and phantom pain after amputation.[18] All were invited to participate in sensory testing of the stump, in addition to answering questionnaires on pain. Inclusion criteria were age more than 18 yr and undergoing amputation of the lower limb. Exclusion criteria were acute amputation, ipsilateral re-amputation, amputation of the foot or toes only, extradural pain treatment started before inclusion, dementia and contraindications to placement of an extradural catheter or combined extradural and general anaesthesia. Informed written consent was obtained from patients and approval was obtained from the regional Ethics Committee and the Danish National Board of Health.

Patients were allocated randomly to one of two groups of equal size. Group 1 (active treatment group) received extradural bupivacaine and morphine before and during amputation and group 2 (control group) received extradural saline and oral–i.m. morphine. Details of randomization have been described previously[18] but briefly patients were stratified on the basis of the intensity of pain before amputation: the first patient entering the study with a pain intensity before amputation of <30 on a visual analogue scale (VAS) (0–100 mm) was assigned to group 1 or 2 by tossing a coin. The next patient with a VAS score <30 was assigned to the opposite treatment. The same procedure was followed for patients with a pain intensity ≥30 on a VAS.

Blindness during the study was ensured by two investigators (L. N. and S. I). L. N. was responsible for the following: recruitment of patients, postoperative pain treatment, and pain assessment and examination of the limb/stump before amputation and after 1 week and 6 months. S. I. was responsible for randomization, placement of extradural catheters, pain treatment from placement of the extradural catheter until the end of anaesthesia, and pain assessment and examination of the limb in the operating theatre. L. N. knew that patients were stratified according to pain intensity before amputation but did not know treatment assignment. For safety reasons the attending nurse anaesthetist was informed of treatment assignment. Otherwise staff and patients were blinded.

PAIN MANAGEMENT AND ANAESTHESIA

Preoperative and intraoperative pain management

In all patients extradural catheters were placed in the L2–3 or L3–4 interspace on the day before amputation and tested using 2% lidocaine with epinephrine 3 ml.

Patients in group 1 received a bolus dose of extradural morphine 2 mg and 0.5% bupivacaine 5–10 ml. If the patient was not free of pain or if sensory block was below or at T12, as assessed by an alcohol wipe, additional 1-ml increments of bupivacaine were given. This was followed by continuous infusion of 0.25% extradural bupivacaine 4–7 ml h^{-1} and morphine 0.16–0.28 mg h^{-1}. Infusion rates were adjusted to individual patient responses (i.e. block level and haemodynamic stability). If the patient reported pain or discomfort in the limb before amputation, infusion rates were increased or additional increments of bupivacaine were given. In the operating theatre and before induction of anaesthesia, a bolus dose of 0.5% bupivacaine 5–15 ml was administered. Further increments were given if sensory block was below or at T12. The degree of motor block after the bolus dose of bupivacaine was assessed on a scale from 0–100.[26] Extradural infusion of bupivacaine and morphine was maintained until the end of anaesthesia. If duration of surgery exceeded 90 min an extra bolus of 0.5% bupivacaine (volume=half the initial bolus dose) was given. All bolus doses of bupivacaine were adjusted to the condition of the patient.

Patients in group 2 received oral or i.m. morphine 5–20 mg, 4–6 times a day, and 5–10 mg on demand and paracetamol 1 g four times daily was given for pain treatment before amputation. The dose of morphine was adjusted to individual needs (i.e. age, weight, present pain and previous consumption of morphine). After placement of the extradural catheter a bolus dose of saline 5 ml was given. This was followed by extradural infusion of saline 4–7 ml h^{-1}, maintained until the end of anaesthesia. Before induction of anaesthesia another bolus of saline 5 ml was given and before the end of anaesthesia a bolus dose of 0.5% bupivacaine 5–10 ml was administered.

In both groups, amputation was performed under general anaesthesia. Premedication comprised diazepam 2.5–20 mg orally, 1–2 h before operation. Anaesthesia was induced with thiopental and maintained with enflurane and nitrous oxide in oxygen. Fentanyl was administered as intermittent bolus doses of 25–100 μg. Atracurium was used to facilitate tracheal intubation and to maintain neuromuscular block. Neuromuscular block was antagonized by neostigmine and atropine. All doses were adjusted according to age, weight and administration of extradural pain.

Postoperative pain treatment

Postoperative pain treatment was similar in the two groups. Bupivacaine 0.25% (3–7 ml h^{-1}) and bolus doses of morphine 2–8 mg, 2–4 times daily were administered extradurally. Infusion rates and doses of morphine were adjusted to individual needs. Infusion of bupivacaine was stopped 2–3 days after amputation, but treatment with extradural morphine was continued for as long as considered necessary. The extradural treatment was supplemented by paracetamol 1 g four times daily.

Pain assessment

Pain was assessed using a VAS (0–100 mm) on the day before amputation (before randomization and before placement of the extradural catheters), in the operating theatre (before administration of the bolus dose of bupivacaine), and after 1 week and 6 months. On the day before amputation, intensity of pain in the limb was recorded. In the operating theatre, pain was assessed by recording mean pain intensity experienced from the time of placement of the extradural catheter until amputation, and at the postoperative interviews, intensities of stump and phantom pain were recorded.

Sensory testing

On the day before amputation (before randomization and before placement of the extradural catheters) pressure pain thresholds, touch and pain detection thresholds, and thermal sensibility were measured. In the operating theatre and after administration of the bolus dose of bupivacaine, pressure pain thresholds were measured. After 1 week and 6 months, pressure pain thresholds, touch and pain detection thresholds, and thermal sensibility were recorded. Also, after 6 months, rates of allodynia and wind-up-like pain were examined. Measurements were performed at the lateral aspect of the limb/stump. If amputation was performed at the thigh or knee, the L2–3 dermatome was examined (above m. vastus lateralis) and if amputation of the calf was performed, the L4 dermatome was examined (above m. tibialis anterior).

Pressure sensibility

Pressure pain threshold (PPT) was determined using a hand-held electronic pressure algometer (Somedic AB, Sweden). The procedure has been described previously.[27] Briefly, a circular probe with an area of 1 cm^2 was used. The pressure application rate was 20 kPa s^{-1}. The patient was told to say "stop" when a sensation of pressure changed to a sensation of pain. This was recorded as PPT and the value on the digital display was read by the examiner. Each value was determined three times with an interval of at least 30 s.

Tactile sensibility

Tactile sensibility was determined using von Frey hairs, consisting of 20 monofilaments of increasing diameter calibrated to deliver a specific force on the skin (Semmes-Weinstein monofilaments, Stoelting, IL, USA). The filaments were applied in an ascending and descending order of magnitude. The force required to bend the filament at the touch detection threshold (TDT) and at the pain detection threshold (PDT) was recorded.

Thermal sensibility

Thermal sensibility was examined using thermal rollers. The rollers were made of steel with steel handles. Sensibility to cold was examined with a thermal roll cooled in a box filled with ice. Sensibility to warmth and heat was examined with thermal rolls heated to 30 and 45°C in a water bath. All sensations were described on a scale from 1 to 9, as reported previously,[28] (1=painful heat, 2=very warm, 3=warm, 4=slightly warm, 5=neutral, 6=slightly cold, 7=cold, 8=very cold, 9=painfully cold).

Wind-up-like pain

Wind-up-like pain was carried out using a procedure described previously by Eide and colleagues.[12] The skin was pricked repeatedly with a von Frey filament (6.65 units=447 g) at a rate of 3 s^{-1}. The stimulation was not painful initially but after a few seconds the patients reported a marked increase in pain. Stimulation was continued for 30 s but discontinued before if the pain became unbearable. Five sites on the stump were stimulated: one site at the end of the stump, and anterior and posterior sites on the lateral and medial aspect of the stump. Wind-up-like pain was considered present if pain could be elicited at at least one site of the stump.

Allodynia

Allodynia was determined by a von Frey hair at the touch detection threshold. The monofilament was moved along the stump and allodynia was considered present if sensation changed from a feeling of touch to a clear sensation of pain.

STATISTICAL ANALYSIS

Results are presented as mean (SD) or median (range). The Mann–Whitney rank sum test was used to analyse differences between medians. Differences between the two groups in postoperative values of PPT, TDT and PDT were analysed as follows: for each patient a standardized value, postoperative/preoperative, was calculated. The standardized values in the two groups were compared on a logarithmic scale (i.e. the values were log-transformed and the mean values in the two groups were compared using a t test and 95% confidence intervals for the difference between means). The estimated mean difference and confidence interval were then transformed back to the original scale, yielding an estimate and 95% confidence interval of the median ratio between the standardized values in the two groups. Fisher's exact test was used to compare rates of allodynia and wind-up-like pain in the two groups. $P<0.05$ was considered significant.

Results

Forty-five patients agreed to participate in sensory examination of the stump: 23 patients in group 1 and 22 in group 2. There were no differences between patients who agreed to take part in sensory testing and those who refused, in age, sex distribution or intensity of pain before amputation (data not shown). There were 31 patients at the 6-month interview: two patients (one from each group) were withdrawn from the study before amputation (in one patient the extradural catheter was displaced accidentally and the other patient only underwent toe amputation); three patients underwent re-amputation (all belonged to group 1) and nine patients died (four in group 1 and five in group 2). Patient characteristics and surgical details are shown in table 1.

PERIOPERATIVE PAIN, AND STUMP AND PHANTOM PAIN AFTER AMPUTATION

Perioperative pain

Median duration of preoperative extradural block (group 1) was 16.5 (range 12–45) h and median duration of postoperative extradural pain treatment (both groups) was 214 (14–756) h.

Table 1 Patient characteristics and surgical details (mean (SD)) (% or number)

	Group 1	Group 2
No. of patients	14	17
Sex (M/F)	6/8	13/4
Age (yr)	61.7 (30.5)	69.2 (10.2)
Diabetes	5	10
Medical treatment because of cardiovascular disease	8	12
Previous contralateral amputation	0	2
Pain at inclusion (VAS 0–100)	61.7 (30.5)	46.1 (29.4)
Daily opioid consumption at admission (mg)	61.4 (45.7)	54.1 (57)
Level of amputation		
Below knee	8	12
Through knee joint	3	0
Above knee	0	5

There was a highly significant difference in pain experienced at the time from placement of the extradural catheter until amputation, between the extradural block and extradural saline groups ($P<0.001$). Eleven of 14 patients in group 1 were pain-free after the extradural pain treatment and scored 0 on a VAS. Two patients continued to have slight and intermittent pain (VAS scores 2 and 4). One patient continued to feel pain despite the extradural treatment. Median intensity of pain in group 1 was 0 (range 0–31). All patients in group 2, except one, had pain during the time from placement of the extradural catheter until amputation. Median pain intensity was 29 (0–80).

Postoperative stump and phantom pain

Details on stump and phantom pain have been presented previously.[2 18] Briefly, there was no difference between the groups at the postoperative interviews when comparing rates of phantom pain. After 1 week the percentage of patients with phantom pain was 57.1% in group 1 and 58.8% in group 2. After 6 months the corresponding values were 78.6% and 58.8% in groups 1 and 2, respectively. Intensities of stump and phantom pain were also similar in the two groups (data not shown).

SENSORY TESTING

It was not possible to perform all types of sensory testing in all patients at all postoperative assessments, mainly because of lack of consent. Obvious contraindications to examination such as delayed healing and infection of the stump occurred in a few cases.

Block before amputation

PPT was examined in 22 patients (nine in group 1 and 13 in group 2) after the bolus dose of bupivacaine in the operating theatre. PPT was not reached by any patient in group 1. To avoid damage to the skin, a cut-off point for PPT was set at twice the value obtained on the day before amputation. Median PPT was 400 (range 300–650) kPa in group 1 and 238 (75–600) kPa in group 2 ($P<0.0001$). The degree of motor block after the bolus dose of bupivacaine before amputation, assessed using the Bromage scale (group 1), was complete (100%) in one patient (unable to move legs or feet), almost complete (66%) in 11 patients (unable to flex knees, but with free movement of feet) and partially complete (33%) in two patients (just able to flex knees, free movement of feet).

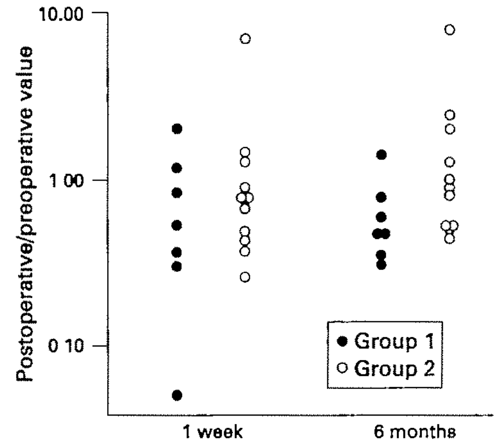

Figure 1 Pressure pain thresholds (PPT) after 1 week and 6 months for groups 1 ($n=7$) and 2 ($n=11$). The standardized value, postoperative/preoperative PPT, is shown for each patient.

Pressure and tactile sensibility

PPT was examined in 18 patients (seven in group 1 and 11 in group 2) on the day before amputation and after 1 week and 6 months. Before amputation, median PPT was 227 kPa in group 1 and 195 kPa in group 2. Figure 1 shows the postoperative PPT values in the two groups. The standardized value, postoperative/preoperative PPT, is presented for each patient. After 1 week the standardized PPT values in group 1 were, on average, 0.59 times the standardized PPT values in group 2 (95% CI 0.21 to 1.66; $P=0.3$). After 6 months the standardized PPT values in group 1 were, on average, 0.51 times the standardized PPT values in group 2 (95% CI 0.24 to 1.1; $P=0.08$)

TDT and PDT were measured in 16 patients (seven in group 1 and nine in group 2). Median TDT and PDT were 0.41 g and 8.51 g, respectively, in group 1 before amputation; corresponding values were 8.51 g and 75.8 g in group 2. Postoperative TDT and PDT values are shown in figure 2. The standardized values, postoperative/preoperative TDT and PDT, are presented for each patient. After 1 week the standardized TDT values in group 1 were, on average, 1.0 times the standardized TDT values in group 2 (95% CI 0.78 to 1.3; $P=0.9$) and the standardized PDT values in group 1 were, on average, 1.3 times the standardized values in group 2 (95% CI 1.0 to 1.6; $P=0.04$). After 6 months the standardized TDT values in group 1 were, on average, 1.2 times the standardized TDT values in group 2 (95% CI 0.89 to 1.59; $P=0.2$) and the standardized PDT values in group 1 were, on average, 1.2 times the standardized values in group 2 (95% CI 0.97 to 1.38; $P=0.09$).

Thermal sensibility

In 15 patients (six in group 1 and nine in group 2), thermal sensibility was measured before amputation, and after 1 week and 6 months. Thermal sensibility

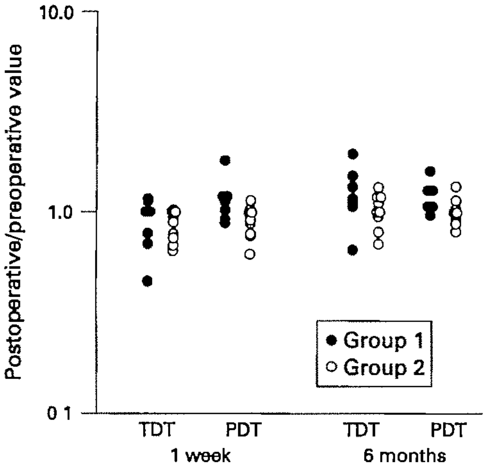

Figure 2 Touch and pain detection thresholds (TDT and PDT) after 1 week and 6 months for groups 1 (n=7) and 2 (n=9). The standardized values, postoperative/preoperative TDT and PDT, are shown for each patient.

was similar in the two groups both before and after amputation. Also, postoperative thermal sensibility was not different from thermal sensibility before amputation (fig. 3).

Wind-up-like pain and allodynia

At the 6-month interview, 19 patients (10 in group 1 and nine in group 2) were examined for wind-up-like pain. Wind-up-like pain was elicited in 11 patients, eight in group 1 and three in group 2 (P=0.07).

The incidence of allodynia was examined in 28 patients after 6 months (12 in group 1 and 16 in group 2). Allodynia was present in nine patients: four in group 1 and five in group 2 (ns). There was no difference between rates of allodynia and wind-up-like pain in the two groups (table 2).

Discussion

In this prospective, randomized study, we found no effect of intense preoperative and intraoperative extradural block on postoperative stump sensibility to mechanical and thermal noxious and non-noxious stimuli. Therefore, our findings suggest that extradural analgesia does not prevent late signs of hyperexcitability at the level of the stump. However, before accepting this notion, some points need consideration.

Table 2 Incidence of wind-up-like pain and allodynia 6 months after amputation (number (%))

	Wind-up-like pain	Allodynia
Group 1		
No. (%)	8 of 10 (80%)	4 of 12 (33.3%)
Group 2		
No. (%)	3 of 9 (33.3%)	5 of 16 (31.3%)

First, it may be argued that selection bias and a limited number of patients were responsible for our negative findings. Although selection bias cannot be excluded, patient characteristics were similar in those who agreed to participate in sensory testing and those who refused. The fact that there was no consistent trend towards an effect of extradural block on stump sensibility after amputation suggests that our failure to find an effect cannot be explained by the small number of patients.

Second, it is possible that central sensitization was not present and therefore could not be blocked. However, pressure pain thresholds were reduced after amputation, and allodynia and wind-up-like pain were present in a relatively large proportion of patients in the block and non-block groups, thus indicating that sensitization to mechanical stimuli was present and amenable to block.

Third, it is also unlikely that our failure to see an effect was a result of selection of stimuli or stimulation of receptors unresponsive to sensitization. We assessed both thermal and mechanical modalities, in addition to different types of mechanical stimuli. Therefore, it is likely that afferent input via C-mechano-heat receptors and low threshold mechano-receptors conveyed by C, Aδ and Aβ fibres, respectively, were examined in this study.

The discrepancy between our findings and those reported in experimental and clinical studies may have several explanations. In experimental studies on the effect of treatment before injury, conditioning stimuli are usually of short duration and may consist of brief C-fibre stimulation,[29] and localized mechanical,[30] thermal[6] or chemical[31] injury.

In studies in human volunteers, different methods of producing hyperalgesia (e.g. localized burn injury or intradermal or topical application of capsaicin) have been used, characterized by producing an afferent C-fibre volley of intense but short duration.[32–34]

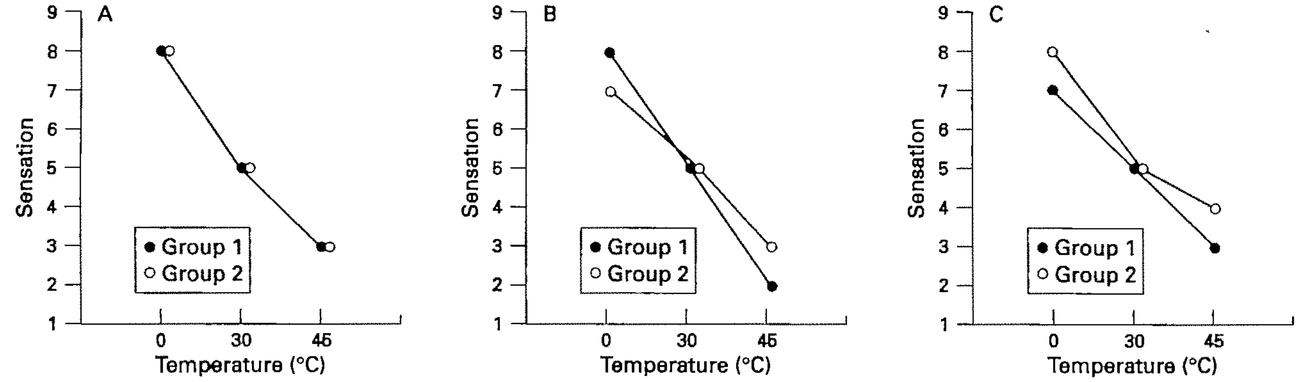

Figure 3 Thermal sensibility in the range 0–45 °C before (A), and 1 week (B) and 6 months (C) after amputation for groups 1 (n=6) and 2 (n=9). All sensations were described on a scale from 1 to 9 (1=painful heat, 2=very warm, 3=warm, 4=slightly warm, 5=neutral, 6=slightly cold, 7=cold, 8=very cold, 9=painfully cold). Values are medians.

In contrast, the nociceptive barrage of the CNS in patients undergoing amputation is intense and long-lasting. We propose that the extradural block in our study was insufficient to block afferent C-fibre input and hence reduce central sensitization. This notion is supported by previous studies. It has been shown that a lumbar extradural block with bupivacaine did not completely prevent impulses, as assessed by somatosensory evoked potentials, in reaching the CNS.[35] Furthermore, Dahl and colleagues[32] found that a short-lasting block of the skin with lidocaine before experimental burn injury postponed but did not prevent secondary hyperalgesia. It may be impossible to prevent afferent input from reaching the CNS during surgery but we cannot exclude the fact that other forms of regional analgesia would be able to influence central sensitization.

Clinical studies have not provided consistent results. In the study of Richmond, Bromley and Woolf,[19] patients undergoing hysterectomy were allocated randomly to one of three groups: morphine 10 mg i.m., 1 h before operation (i.m. pre) (n=8), morphine i.v. at induction of anaesthesia (i.v. pre) (n=7) or morphine i.v. at closure of the peritoneum (i.v. post) (n=12). Pain sensitivity around the wound, as assessed by von Frey hair, was reduced after 24 and 48 h in both preoperative treatment groups compared with the i.v. post group. Tverskoy and colleagues[20] found that pre- and intraoperative administration of morphine (n=9) or ketamine (n=9) reduced the intensity of pain to suprathreshold pressure on the wound 48 h after hysterectomy. The effect of ketamine on postoperative hyperalgesia was studied[21] and the area of hyperalgesia was reduced in 10 patients who received ketamine during and for 72 h after nephrectomy compared with 10 patients who received placebo. Johansson and colleagues[36] examined 66 patients undergoing cholecystectomy. The abdominal wall was infiltrated with ropivacaine or saline before surgical incision. The pressure exerted to reach maximum pain tolerance was assessed at intervals for 7 days after operation. The only difference between the two groups was after 6 h, which could be explained by a residual effect of ropivacaine.

The difference between our results and those of others[19,20] may have several explanations. Other workers have studied only early postoperative hyperalgesia, and differences in the extent of surgical trauma, patient categories and methods of assessment may also play a role. The positive findings in the study by Stubhaug and colleagues[21] may be explained by the use of an N-methyl D-aspartate (NMDA) receptor antagonist as the NMDA receptor is known to be involved in central hyperexcitability.[37–39]

After amputation, neuromas of the nerve endings are formed. Such neuromas display a series of abnormalities, including spontaneous activity[40] and increased sensitivity to chemical, mechanical and metabolic factors.[41] Axotomized cell bodies in dorsal root ganglia may also show abnormal spontaneous activity[42] so that dorsal horn neurones receive abnormal input from axotomized nerve endings and from sensitized dorsal root ganglion cells. In our study, it is likely that the afferent barrage from the periphery outlasted postoperative extradural block and thus induced or maintained central sensitization beyond the early postoperative period.

In summary, while there is circumstantial evidence from experimental and clinical studies that analgesic treatment before injury prevents pain and hyperalgesia, our study suggested that preoperative and intraoperative extradural block had no long-term prophylactic effect on hyperalgesia, allodynia and wind-up-like pain.

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British Journal of Anaesthesia 1998; **81**: 355–357

Does speed of intrathecal injection affect the distribution of 0.5% hyperbaric bupivacaine?

A. Casati, G. Fanelli, G. Cappelleri, A. Leoni, M. Berti, G. Aldegheri and G. Torri

Summary

We have evaluated the influence of speed of intrathecal injection on lateral distribution of 0.5% hyperbaric bupivacaine. We studied 60 patients undergoing lower limb surgery who were placed in the lateral position with the operative side in the dependent position. After dural puncture (25-gauge Whitacre spinal needle), the needle aperture was turned towards the dependent side and 0.5% hyperbaric bupivacaine 8 mg was injected randomly at a rate of 0.02 ml s^{-1} (group slow, n=30) or 0.25 ml s^{-1} (group fast, n=30). Lateral position was maintained for 15 min while a blinded observer recorded loss of pinprick sensation and degree of motor block on both surgical and non-surgical sides. There were no differences between the groups. Forty-five minutes after patients were turned to the supine position, spinal anaesthesia was unilateral in 17 patients in group slow (56%) and in 13 patients in group fast (43%). We conclude that using extremely low speeds for intrathecal injection were not clinically advantageous in obtaining unilateral spinal anaesthesia. (*Br. J. Anaesth.* 1998; **81**: 355–357).

Keywords: anaesthesia, subarachnoid; anaesthetics local, bupivacaine

Unilateral spinal block may be of use to practitioners faced routinely with unilateral orthopaedic surgery involving the lower limbs, as this technique may attenuate the haemodynamic effects of spinal anaesthesia.[1] However, conflicting results can be found in the literature.[1-3] Low anaesthetic dose and pencil-point design of spinal needle tips have been demonstrated to be important factors in producing unilateral spinal anaesthesia,[1 4] while injection of hyperbaric solutions at very low speed ($\leq$0.1 ml s^{-1}) through a pencil-point needle is known to produce a uniform stream, which should minimize mixing of the anaesthetic solution with cerebrospinal fluid.[5 6]

The aim of our investigation was to evaluate the effects of different speeds of intrathecal injection on the distribution of a relatively small dose of 0.5% hyperbaric bupivacaine in a prospective, double-blind study.

Patients and methods

The study was approved by the Hospital Ethics Committee and informed consent was obtained from each patient. In a pilot study we observed an incidence of unilateral spinal anaesthesia of 60%; as we wished to detect a 20% difference in the rate of unilateral spinal anaesthesia accepting an α error of 5% and a β error of 20%, the required study size was 30 patients per group.[7] We studied 60 ASA I–II patients, aged 25–65 yr, undergoing spinal anaesthesia for elective orthopaedic surgery involving a lower limb (e.g. toe, foot and ankle repair, in addition to knee and ankle arthroscopy). Patients receiving regular analgesic therapy and those with marked scoliosis, diabetes or peripheral neuropathy were excluded.

On arrival in the operating theatre, a standard i.v. infusion of lactate Ringer's solution 7 ml kg^{-1} was given. No premedication was administered before the block. Standard ASA monitoring was used, including non-invasive arterial pressure, heart rate and pulse oximetry.

Patients were placed in the lateral position with the limb to be operated on in the dependent position and the vertebral column kept as horizontal as possible by tilting the operating table or placing a pillow under the shoulder. Dural puncture was performed at the L3–4 interspace using the midline approach with a 25-gauge Whitacre spinal needle (Becton-Dickinson, NJ, USA). After free flow of cerebrospinal fluid (CSF) was observed, the needle aperture was turned towards the dependent side of the spinal canal and 0.5% hyperbaric bupivacaine 8 mg (Marcaine Spinal Heavy, Astra, Sweden) was injected. No aspiration of cerebrospinal fluid was performed either during or at the end of injection of local anaesthetic. According to a sealed envelope technique, patients were allocated randomly to one of two groups: in group slow (n=30), the local anaesthetic solution was injected at a speed of approximately 0.02 ml s^{-1} (1.6 ml injected over 80 s); in group fast (n=30) the local anaesthetic was injected at a speed of approximately 0.25 ml s^{-1} (1.6 ml injected over 6 s).

The lateral position was maintained for 15 min, then patients were turned to the supine position. Oxygen was administered by face mask if required. Hypotension, defined as systolic arterial pressure 30% less than baseline values, was treated with rapid i.v. infusion of lactate Ringer's solution 250 ml/5 min. If this proved ineffective, an i.v. bolus of ephedrine 5 mg was given. Bradycardia (<45 beat min^{-1}) was treated with i.v. atropine 0.5 mg.

An observer, blinded to the speed of intrathecal injection, evaluated the evolution of sensory and

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motor blocks on both surgical and non-surgical sides. Sensory block was evaluated by loss of pinprick sensation (20-gauge hypodermic needle), while a modified Bromage scale was used for motor block evaluation (0=no motor block; 1=hip blocked; 2=hip and knee blocked; 3=hip, knee and foot blocked). Sensory and motor blocks were tested every 3 min after injection of bupivacaine until patients were turned to the supine position, and then every 5 min until the point of regression of sensory level by two segments on the surgical side. Further testing was performed every 15 min until the point of regression of motor block by one degree on the surgical side.

The quality of spinal block was judged according to the need for supplementary i.v. analgesics and sedation: satisfactory spinal anaesthesia=neither i.v. fentanyl nor sedation; unsatisfactory spinal anaesthesia=need for additional i.v. fentanyl ≥0.1 mg and sedation (continuous i.v. propofol infusion 2 mg kg^{-1} h^{-1}); failed spinal anaesthesia=general anaesthesia. The occurrence of postoperative headache, and pain or dysaesthesia, or both, in the buttocks, thighs or lower limbs was evaluated 24 h after dural puncture by the anaesthetist, and 1 week after operation during the first routine surgical visit by the surgeon.

Statistical analysis was performed using the program Stat-view 3.0 (Abacus Conc., USA). The Mann–Whitney *U* test was used to analyse differences between the two groups; the Wilcoxon test was used to analyse differences within groups. Contingency table analysis or Fisher's exact test were also used as indicated. $P<0.05$ was considered significant. Results are presented as median (range) or as number (%).

Results

The two groups were comparable in age, weight, height, ASA status, male to female ratio, duration of surgery and tourniquet times (table 1).

Table 1 Patient characteristics (mean (SD) or median (range)) in the two groups. No significant differences

	Group slow (*n*=30)	Group fast (*n*=30)
Age (yr) (mean (range))	44 (24–65)	48 (29–65)
Weight (kg)	67 (13)	68 (11)
Height (cm)	169 (6)	165 (6)
ASA status	I (I–II)	I (I–II)
Sex (M/F)	8/22	11/19
Duration of surgery (min)	64 (21)	75 (28)
Tourniquet time (min)	59 (19)	57 (26)

No patient required general anaesthesia; one patient in group fast complained of pain as a result of thigh tourniquet 40 min after dural puncture, and required additional analgesia (unsatisfactory spinal anaesthesia). No differences in the incidence of hypotension were observed between the groups: one patient in group slow and two patients in group fast required i.v. ephedrine (ns).

The main results are summarized in table 2. The highest level of sensory block on both surgical and non-surgical sides, and times to reach it, in addition to times for regression of sensory level by two segments, and times for regression of motor block by one degree, were similar in the two groups. The incidence of unilateral sensory and motor blocks at the end of the 15 min in the lateral position and 30 min after patients were turned supine (45 min after injection of bupivacaine) was slightly higher in group slow than in group fast (ns).

Figure 1 shows the evolution of sensory block on both surgical and non-surgical sides in the two groups of patients. Three patients (two in group slow and one in group fast) showed loss of pinprick sensation below T12 at the end of the 15 min in the lateral position. However, after patients were turned to the supine position, the final sensory level increased to T10 and T11 in the two patients in group slow, and to T8 in the patient in group fast. Although group fast showed a wider range of sensory block on both surgical and non-surgical sides compared with group slow, median values were not significantly different. There was a significant difference between surgical and non-surgical sides throughout the study within each group.

No urinary retention was observed in any patient, and postoperative follow-up revealed no neurological complications or post-dural puncture headache.

Discussion

We have demonstrated that intrathecal injection at an extremely low speed did not improve the rate of unilateral spinal anaesthesia. No differences in the characteristics of conventional bilateral spinal anaesthesia have been reported when injecting either isobaric[8] or hyperbaric[9] anaesthetic solutions at different speeds. However, the Whitacre spinal needle has been demonstrated to provide a non-turbulent uniform stream at 35° to the longitudinal axis when using a low speed of injection (≤ 0.025 ml s^{-1}), and a violent stream with instant dispersion and mean angle of exit of 40° using an injection speed of 0.25 ml s^{-1}.[5 6] This

Table 2 Sensory levels and motor block in the two groups. Data are median (range) or number (%). ***$P<0.001$ compared with surgical side

	Group slow (*n*=30)	Group fast (*n*=30)
Highest sensory level (surgical side)	T 8 (T 12–T 4)	T 10 (T 12–T 3)
Highest sensory level (non-surgical side)	L 1 (/–T 4)***	L 2 (/–T 4)***
Time to highest sensory level (surgical side)	25 (9–35)	20 (6–35)
Time to regression of sensory level by two segments	82 (40–135)	75 (30–125)
Time to regression of motor block by one degree	120 (75–165)	110 (45–180)
Patients with unilateral sensory block—lateral (15 min)	22 (73%)	18 (60%)
Patients with unilateral motor block—lateral (15 min)	25 (83%)	25 (83%)
Patients with unilateral sensory block—supine (45 min)	17 (56%)	13 (43%)
Patients with unilateral motor block—supine (45 min)	24 (80%)	19 (63%)

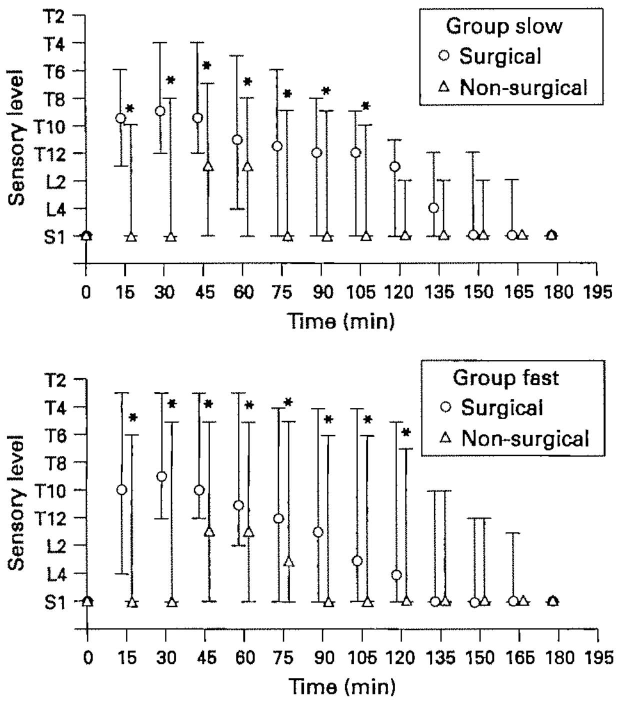

Figure 1 Evolution of median (range) sensory level (loss of pinprick sensation) on both surgical and non-surgical sides after administration of 0.5% hyperbaric bupivacaine 8 mg injected at a speed of 0.02 ml s^{-1} (group slow, n=30) or 0.25 ml s^{-1} (group fast, n=30). No significant differences between groups

suggested that low speed intrathecal injection would minimize the mixing of hyperbaric bupivacaine with CSF, improving unilateral distribution of spinal block. However, our results failed to confirm this.

The incidence of unilateral spinal anaesthesia observed in our study was quite different from that reported after injection of 12 mg of hyperbaric tetracaine through a Quincke needle.[2 3] The anaesthetic dose is crucial in this regard,[1 4 10] and a close correlation between dose of anaesthetic and incidence of sensory block has been demonstrated.[4] A small dose can increase the failure rate of spinal anaesthesia.[1] In our study we used the intermediate dose (8 mg) of hyperbaric bupivacaine, which probably reduced the rate of unilateral block compared with previous studies,[1 4] but provided successful spinal anaesthesia in more than 98% of patients, with unilateral block 30 min after patients were turned supine in 43–56% of patients.

Similar to previous reports,[11 12] our results showed that the median time for regression of sensory level by two segments after administration of hyperbaric bupivacaine 8 mg was 75–82 min, and the median time for regression of motor block by one degree was 110–120 min.

Pencil-point spinal needles and extremely low speeds of injection have been reported as contributing factors in transient radicular irritation when highly concentrated hyperbaric lidocaine is used.[13] The record of neurotoxicity after spinal bupivacaine has remained relatively untainted compared with both lidocaine and mepivacaine,[14 15] and no neurological deficit after anaesthesia was observed in our study. However, we believe that using extremely low speeds for intrathecal injection should not be advocated when attempting unilateral spinal anaesthesia, as no clinical advantages are provided.

In summary, the adverse haemodynamic effects of spinal block may be mitigated during unilateral spinal anaesthesia, as the reduced extent of sensory block could theoretically be associated with a lower degree of sympathetic block.[16 17] In our study, severe hypotension was observed in only 5% of patients, less than that reported during conventional bilateral spinal anaesthesia.[18] Further sufficiently powerful studies should be performed to evaluate the potential haemodynamic benefit of this anaesthetic technique.

We conclude that using extremely low speeds for intrathecal injection were not clinically advantageous in obtaining unilateral spinal anaesthesia.

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Effect of nimodipine on regression of spinal analgesia

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Summary

We have investigated the effect of infusion of nimodipine on the spread of spinal anaesthesia in 50 patients undergoing transurethral procedures. Patients were allocated randomly to receive during operation continuous infusion of nimodipine 10 ml h^{-1} (group N, n=25) or normal saline (group C, n=25) in a double-blind manner. All patients received hyperbaric lidocaine 100 mg (5% in 8% dextrose) intrathecally and were then placed in the lithotomy position. Twenty minutes after intrathecal injection the level of spinal anaesthesia was tested with a pressure palpator and a baseline was established. Assessments were repeated 5, 10 and 15 min thereafter. Five minutes after establishing baseline, mean regression of sensory analgesia did not differ between groups. Analgesia had regressed by 1.3 (SD 1.4) and 1.0 (1.9) cm, respectively. After 10 min, sensory block in group N regressed by 1.7 (1.7) cm and in group C by 1.5 (1.6) cm. After 15 min these values were 1.1 (1.7) cm and 2.2 (1.9) cm, respectively (P<0.035). Similar results were found after normalizing the changes by dividing the change by patient height. (*Br. J. Anaesth.* 1998; **81**: 358–360).

Keywords: anaesthetic techniques, subarachnoid; anaesthetics local, lidocaine; calcium channel block, nimodipine

Previous studies have shown that systemic opioids and inhalation of 50% nitrous oxide enhance the level or delay regression of subarachnoid analgesia.[1-4] Calcium is involved in endogenous regulation of pain sensitivity and substances with calcium channel blocking effect have antinociceptive properties.[5]

We have investigated the effect of continuous infusion of nimodipine on the level of spinal analgesia produced by hyperbaric lidocaine.

Patients and methods

After obtaining approval from the Ethics Committee and informed patient consent, we studied 50 male patients, ASA II–III, undergoing elective transurethral prostatectomy or transurethral resection of bladder papillomas. Exclusion criteria were central nervous system disorders, intake of analgesics or drugs which may interact with analgesics, and hearing impairment. Patients were visited the day before surgery and the procedure of assessing the level of spinal analgesia was explained. Premedication was not given.

In the operating room, patients were allocated randomly to receive nimodipine (n=25) or normal saline (control group, n=25) in a double-blind manner. ECG, heart rate, arterial pressure (oscillotonometer) and Sp_{O_2} were monitored. Two peripheral 17-gauge i.v cannulae were inserted, one to administer Ringer's lactated solution and the other connected to an infusion pump (DSP, Johnson and Johnson) to administer normal saline or nimodipine 10 ml h^{-1} (1 ml=0.2 mg). Infusion of nimodipine or normal saline was started before subarachnoid injection of lidocaine.

After local infiltration of the skin with 2% lidocaine, hyperbaric lidocaine 100 mg (2 ml of 5% lidocaine in 8% dextrose) was injected into the subarachnoid space. All lumbar punctures were performed in the L3–4 interspace using a 25-gauge Whitacre needle and with the patient lying in the left lateral position. Surgery and assessments of level of spinal analgesia were performed with the patient in the lithotomy position.

Twenty minutes after subarachnoid injection the level of sensory block was assessed from a caudad to a cephalad direction using a pressure palpator (Pressure FEELER 650 g Sedatelec, Chemin des Muriers, F-69540 Irigny, France).[4] A baseline level of block was determined 20 min after subarachnoid injection of lidocaine because at that time maximal spread of spinal anaesthesia is usually obtained.[6] Four points lying on the left posterior, middle and anterior axillary lines, and on the line 4–5 cm medial to the left anterior axillary line at which patients responded to the palpator were located and marked as the baseline of sensory block. The procedure of establishing baseline and assessing the changes in spinal analgesia has been described elsewhere.[1 4]

Sensory block was assessed in each group 5, 10 and 15 min after establishing baseline. Systolic (SAP) and diastolic (DAP) arterial pressures, and heart rate (HR) were recorded before and immediately after spinal anaesthesia, when baseline sensory block was established, and 5, 10 and 15 min thereafter. Nimodipine or normal saline was prepared by

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Table 1 Changes in sensory block (cm) and values adjusted for height (cm/h) in the nimodipine and control groups 5, 10 and 15 min after establishing baseline sensory block. Values are mean (SD). *$P<0.05$ between groups

	Nimodipine group		Control group	
Time after baseline (min)	cm	cm/ht×10^{-3}(cm)	cm	cm/ht×10^{-3}(cm)
5	−1.3 (1.4)	−7 (8)	−1.0 (1.9)	−6.0 (11)
10	−1.7 (1.7)	−11 (10)	−1.5 (1.6)	−9 (10)
15	−1.1 (1.7)*	−7 (10)*	−2.2 (1.9)	−13 (11)

Table 2 Systolic (SAP) and diastolic (DAP) arterial pressures, and heart rate (HR) before and after spinal anaesthesia, and 0, 5, 10 and 15 min after establishing baseline sensory block in the nimodipine (N) and normal saline (C) groups Values are mean (SD). No significant differences

	SAP		DAP		HR	
	Group N	Group C	Group N	Group C	Group N	Group C
Before spinal	154 (28)	149 (27)	89 (13)	82 (13)	74 (12)	77 (14)
After spinal	146 (24)	147 (26)	83 (12)	81 (12)	75 (13)	75 (13)
0 min before baseline	125 (19)	128 (24)	72 (11)	73 (14)	74 (14)	68 (17)
5 min after baseline	122 (17)	127 (25)	71 (10)	76 (14)	70 (12)	65 (15)
10 min after baseline	120 (18)	127 (23)	69 (11)	76 (13)	68 (13)	64 (14)
15 min after baseline	120 (21)	127 (24)	69 (12)	75 (12)	66 (11)	65 (14)

an anaesthetist who was not involved in administering anaesthesia or assessing the level of spinal analgesia. Thirty-five minutes after subarachnoid injection of lidocaine and 15 min after establishing baseline, when measurements were completed, infusion of nimodipine or normal saline was discontinued.

As patient height ranged from 155 to 185 cm, we adjusted the loss of level of analgesia (in cm) by dividing by patient height. Patient data, changes in the level of sensory block and haemodynamic changes at the predetermined times between the two groups were compared using the unpaired Student' s *t*-test.

Results

Patient characteristics and volume of solution administered during operation were similar between groups. Mean age, body weight and height were 71 (range 53–85) yr, 72 (SD 14) kg and 166 (SD 10) cm, and 72 (53–88) yr, 73 (13) kg and 166 (7) cm in the nimodipine and control groups, respectively. Mean volumes administered were nimodipine 7.3 (SD 0.9) ml (1.5 mg) and normal saline 7.2 (0.7) ml.

Five minutes after establishing baseline, similar regression of the level of sensory block was found in the nimodipine and control groups. At this point the 95% limits of confidence for the nimodipine group were −1.843 and −0.699, and −1.797 and −0.202 for the control group. Ten minutes after defining baseline, the level of sensory analgesia regressed further in both groups. The 95% limits of confidence were −2.443 to −1.057 and −2.139 to −0.801 in the nimodipine and control groups, respectively. However, at 15 min, regression differed significantly between the two groups, being two-fold greater in the control group (P=0.038); the 95% limits of confidence were −1.853 and −0.446 in the nimodipine group and −3.00 and −1.453 in the control group (table 1).

After adjusting for height, the differences were consistent with the raw data and significant 15 min after baseline (P=0.035) (table 1). SAP, DAP and HR did not differ between groups at any time (table 2).

Discussion

This study has shown that i.v. infusion of nimodipine was associated with a delay in regression of sensory block produced by intrathecal injection of lidocaine.

Previous studies have shown that systemic administration of opioids or inhalation of 50% nitrous oxide enhanced the spread of spinal analgesia or delayed its regression.[1–4] Opioids and nitrous oxide may alter the pain process at a supraspinal level by disinhibiting neurones in the rostral ventromedial medulla.[1 2 4 7] In contrast, tenoxicam, a non-steroid anti-inflammatory analgesic, had no effect on the spread of spinal analgesia.[8] This drug has a very low lipophilicity and concentrations in the central nervous system are negligible.

Nifedipine given extradurally in rats has analgesic properties and it has been suggested that the antinociceptive effect is regulated by spinal rather than supraspinal mechanisms.[9]

Calcium channel antagonists interfere with the action of local anaesthetics. In rats, verapamil given intrathecally potentiated spinal anaesthesia produced by lidocaine or tetracaine.[10] Intrathecal verapamil alone did not produce motor or sensory block but in combination with lidocaine or tetracaine, the block produced was more potent and of longer duration than that produced by the local anaesthetic alone.[10] Iwasaki and colleagues demonstrated in rats that local sensory block produced by lidocaine injection at the tail base was potentiated by verapamil, diltiazem and nicardipine in a dose-dependent manner.[11]

In a laboratory study, Sugiyama and Muteki showed that tetracaine, at concentrations required for spinal anaesthesia, depressed high and low voltage-activated calcium channels of dorsal root ganglion cells of rat sensory neurones, the most susceptible being the L-type calcium channel.[12] The anaesthetic potencies of local anaesthetics correlate well with their potencies in inhibiting calcium influx via voltage-gated channels. Therefore, inhibition of calcium influx via voltage-gated calcium channels resulting in inhibition of calcium-dependent biochemical processes may contribute to the mechanisms of spinal anaesthesia.[12] Hirota and colleagues studied the effect of procaine, prilocaine, lidocaine, bupivacaine, amylocaine and R(+) and S(–) ropivacaine on L-type voltage-activated calcium channels in cerebrocortical membranes prepared from rat brains. They found an interaction between local anaesthetic agents and the L-type calcium channel.[13]

In one clinical study, systemic nifedipine potentiated extradural morphine-induced analgesia,[14] but this was accompanied by significant decreases in arterial pressure. In our study, nimodipine did not produce hypotension. However, the lithotomy position after spinal anaesthesia attenuates the decrease in arterial pressure,[15] and this position may have contributed to the haemodynamic stability of our patients.

Our data support the experimental data, suggesting a contribution of voltage-activated calcium channels to the nociception process. In our study, the delay in regression of spinal analgesia associated with nimodipine had statistical, but probably not clinical, significance. In contrast with fentanyl or nitrous oxide, administration of nimodipine is not recommended to enhance or delay regression of spinal block. However, patients treated with calcium antagonists may exhibit delayed regression of sensory block after spinal analgesia. For this reason, when the pharmacodynamics of local anaesthetics are studied, patients receiving calcium antagonists should be excluded.

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An open, randomized comparison of alfentanil, remifentanil and alfentanil followed by remifentanil in anaesthesia for craniotomy

J. R SNEYD, A. WHALEY, H. L. DIMPEL AND C. J. H. ANDREWS

Summary

We studied 52 adults undergoing elective craniotomy, allocated randomly to one of three opioid treatments: alfentanil 50 μg kg^{-1} followed by 0.833 μg kg^{-1} min^{-1} until dural closure (group Alf.); alfentanil 50 μg kg^{-1} followed by 0.833 μg kg^{-1} min^{-1} for 2 h, then remifentanil 0.25 μg kg^{-1} min^{-1} (group Alf.–Remi.); or remifentanil 1 μg kg^{-1} followed by 0.5 μg kg^{-1} min^{-1} reducing to 0.25 μg kg^{-1} min^{-1} after craniotomy (group Remi.). Anaesthesia was maintained with infusion of propofol and 66% nitrous oxide in oxygen. Infusions of propofol and remifentanil were stopped at head bandaging. Group Remi. had the least intraoperative haemodynamic responses and group Alf. the most (P<0.05). Times to tracheal extubation and obey commands were similar in all groups. In all patients in group Alf.–Remi. and group Remi., the trachea was extubated 27 min from the end of anaesthesia; three patients in group Alf. were slower to recover. Use of analgesia in the recovery room and time to transfer to the neurosurgical unit were similar in the three groups. (*Br. J. Anaesth.* 1998; **81**: 361–364).

Keywords: analgesics opioid, alfentanil; analgesics opioid, remifentanil; surgery, neurological; pharmacokinetics, alfentanil; pharmacokinetics, remifentanil

Remifentanil is a new opioid analgesic with similar pharmacodynamic effects to alfentanil. Preliminary reports suggest that remifentanil does not alter cerebral blood flow carbon dioxide reactivity[1] and has minimal effects on intracranial pressure and cerebral blood flow.[2]

We have reported previously pharmacokinetic simulations which suggested that sequential administration of a less expensive longer lasting opioid followed by terminal infusion of remifentanil might preserve the rapid early wakening associated with remifentanil while providing satisfactory intraoperative conditions and early recovery.[3 4] We report a preliminary controlled study which evaluated the sequential alfentanil–remifentanil technique.

Patients and methods

Adult patients undergoing elective craniotomy gave written informed consent to participate in the study which was approved by the local Ethics Committee.

OPIOID TREATMENTS AND ANAESTHESIA

Shortly before anaesthesia, patients were allocated randomly to one of three opioid treatments using sealed envelopes containing treatment codes generated by a computer program (Excel 5.0a, Microsoft Inc.). Group Alf. received a bolus injection of alfentanil 50 μg kg^{-1} followed by an infusion of 0.833 μg kg^{-1} min^{-1} until the start of dural closure. Group Alf.–Remi. received sequential treatment with two opioids: after an initial bolus of alfentanil 50 μg kg^{-1}, an infusion of alfentanil 0.833 μg kg^{-1} min^{-1} was continued for 2 h, when it was stopped and replaced by infusion of remifentanil 0.25 μg kg^{-1} min^{-1}. Group Remi. received a bolus injection of remifentanil 1 μg kg^{-1} followed by an infusion of 0.5 μg kg^{-1} min^{-1} reducing to 0.25 μg kg^{-1} min^{-1} after craniotomy. All patients received propofol for induction of anaesthesia (0.5 mg kg^{-1} bolus and 10 mg every 10 s until anaesthetized) and 100 μg kg^{-1} min^{-1} until dural closure, reducing by 16.7 μg kg^{-1} min^{-1} every 10 min thereafter to a minimum of 50 μg kg^{-1} min^{-1}. Neuromuscular block was achieved with atracurium and the lungs were ventilated to an end-tidal carbon dioxide partial pressure of 4.5–5 kPa with 66% nitrous oxide in oxygen. Infusions of propofol and remifentanil were stopped at head bandaging.

The mean rates of administration of propofol, alfentanil and remifentanil were calculated by dividing the total dose of drug administered by the time over which it was given. Times to adequate spontaneous respiration (judged clinically), extubation and to obey a verbal command were recorded.

HAEMODYNAMIC RESPONSES AND HYPOTENSION

An adverse haemodynamic response was defined as mean arterial pressure >100 mm Hg or heart rate >90 beat min^{-1}. These were treated with alfentanil 15 μg kg^{-1} (group Alf. and group Alf.–Remi. in the first 2 h) or remifentanil 1 μg kg^{-1} and an increase in the infusion rate of 0.125 μg kg^{-1} min^{-1} (group Remi. and group Alf.–Remi. after 2 h). If hypertension or tachycardia was present 2 min later, the treatment was repeated (and the infusion rate of alfentanil increased by 0.25 μg kg^{-1} min^{-1} in group Alf. or group Alf.–Remi. in the first 2 h). If the haemodynamic

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Table 1 Patient chracteristics, duration of anaesthesia and drug administration rates (mean (SD)), median (range) or number)

	Group Alf.	Group Alf.–Remi.	Group Remi.
Age (yr)	53.8 (14.6)	49.6 (13.5)	53.1 (11.8)
Sex (M:F)	7:12	11:5	4:13
Weight (kg)	70.5 (13.4)	75.4 (13.7)	68.5 (15.9)
Duration of anaesthesia (min)	206 (101–337)	210 (137–689)	201 (113–558)
Propofol administration (μg kg^{-1} min)	87.7 (15.0)	85.8 (15.7)	80.7 (10.7)
Alfentanil administration (μg kg^{-1} h^{-1})	1.37 (0.48)	1.50 (0.25)	
Remifentanil administration (μg kg^{-1} min^{-1})		0.27 (0.08)	0.37 (0.06)

response persisted for another 2 min, the infusion rate of propofol was increased by 33.3 μg kg^{-1} min^{-1}. In group Alf., haemodynamic responses occurring after alfentanil had been discontinued were treated with labetolol or hydralazine. If clinically appropriate, infusion rates which had been increased were subsequently reduced at the anaesthetist's discretion. For hypotensive episodes (mean arterial pressure <60 mm Hg) which did not respond to a fluid bolus, the infusion rate of propofol was reduced. The number of haemodynamic responses and hypotensive episodes were recorded.

MANAGEMENT AFTER SURGERY

Between the end of anaesthesia and subsequent discharge from the recovery room, analgesia was provided with morphine 2 mg i.v. at 5-min intervals as necessary to a maximum dose of 10 mg. If a patient became hypertensive despite apparently adequate analgesia, labetolol or hydralazine was administered. Administration of morphine and discharge from the recovery room were at the discretion of the nursing staff who were blinded to the opioid treatment. Use of morphine, antihypertensive agents and time of discharge from the recovery area to the neurosurgical intensive care unit were recorded.

STATISTICAL ANALYSIS

Statistical analysis was performed using Excel 5.0a (Microsoft Inc.) and Statview 4.01 (Abacus Concepts Inc.) on an Apple Macintosh 7100/80 computer running operating system B1–7.5. Duration of anaesthesia, recovery times and recovery room discharge times were compared using the Kruskal–Wallis test. Drug administration rates were calculated from the total amount of drug given and were compared using unpaired *t* tests. Haemodynamic responses, requirement for analgesia and hypotensive episodes were compared using the chi-square test. $P<0.05$ was considered significant.

Results

We approached 57 patients to participate in the study and 53 consented. After surgical difficulties, one patient in group Alf.–Remi. received intraoperative thiopental and underwent elective ventilation after surgery. Data from this patient were excluded. Therefore, we present an analysis of data from 52 patients.

Two patients in group Alf.–Remi. had shorter operations than envisaged, with dural closure commencing within 2 h of the start of anaesthesia (i.e. the alfentanil infusion was still running and remifentanil had not been started). In these cases infusion of alfentanil was stopped and no remifentanil was given. Data from these patients were analysed on an "intention to treat" basis and included in group Alf.–Remi. One patient in group Alf. did not recover from surgery and required artificial ventilation for more than 48 h. Data from this patient were included in the analysis of intraoperative characteristics but excluded from analysis of recovery from anaesthesia.

Although we had intended to study 100 patients, the study was terminated after recruiting 53 patients because of investigator dissatisfaction with the relatively slow recovery of some patients and a clinical impression that the use of nitrous oxide and a propofol infusion of 100 μg kg^{-1} min^{-1} provided an excessively hypnotic component to the anaesthetic.

The treatment groups were similar in age, weight and duration of anaesthesia, although there were mostly males in group Alf.–Remi. and mostly females in group Alf. and group Remi. (table 1).

HAEMODYNAMIC STABILITY AND ANALGESIA

The number of patients with haemodynamic responses during the period of opioid infusion and total number of responses varied significantly between groups, with group Remi. having the least responses and group Alf. the most (table 2). The use of labetolol or hydralazine as antihypertensive treatments after cessation of opioid infusion and the use of morphine analgesia in the recovery area did not vary significantly between groups (table 2).

RECOVERY FROM ANAESTHESIA

Median times to tracheal extubation and obey commands were similar in all three groups (table 3). In all patients in group Alf.–Remi. and group Remi., the trachea was extubated 27 min from the end of anaesthesia. Three patients in group Alf. were slower to recover (fig. 1). The total anaesthesia times for these three patients were not especially prolonged (191, 236 and 251 min). The process of recovery was qualitatively different in group Remi., with patients emerging suddenly with near synchronous return of respiration, tracheal extubation and response to commands (table 3).

Times to discharge from the recovery room to the

Table 2 Haemodynamic responses during opioid infusion (mean arterial pressure >100 mm Hg or heart rate > 90 beat min^{-1}), hypotension (mean arterial pressure <60 mm Hg at any time during anaesthesia) and use of antihypertensive agents and analgesia. Data are number of patients (number of episodes)

	Group Alf.	Group Alf.–Remi	Group Remi	*P* value (chi-square test)
Haemodynamic responses	15 (33)	9 (33)	3 (8)	<0.01
Hypotension	13 (26)	9 (23)	13 (37)	0.76
Use of antihypertensive agents	11	6	8	0.67
Use of analgesia in recovery room	10	8	11	0.84

Table 3 Recovery from anaesthesia and discharge from recovery room to the neurosurgical unit. Times are median (range) from discontinuation of propofol and nitrous oxide. There were no significant differences between groups (Kruskal–Wallis test)

	Group Alf.	Group Alf.–Remi.	Group Remi.
Adequate respiration (min)	10 (0–46)	13 (6–27)	11 (7–18)
Tracheal extubation (min)	14 (7–48)	16 (6–27)	11 (9–21)
Obey verbal command (min)	16 (6–123)	19.5 (6–63)	12.5 (7–50)
Discharge from recovery room (min)	119 (86–225)	111 (45–243)	111.5 (58–158)

neurosurgical unit were similar in the three groups (table 3).

Discussion

We have compared remifentanil and alfentanil and evaluated a sequential infusion scheme. We did not demonstrate significant benefit in terms of recovery from anaesthesia with remifentanil compared with alfentanil and in this context the sequential scheme was difficult to evaluate. Nevertheless, remifentanil reduced the number of haemodynamic responses without excess hypotension. Haemodynamic stability is desirable in neuroanaesthesia and this effect may be clinically important.

Guy and colleagues[1] conducted a double-blind comparison of fentanyl and remifentanil during long neurosurgical procedures (mean duration 6 h) and reported that intracranial pressure and cerebral perfusion pressure were similar in the two groups and both recovered rapidly with a median time to tracheal extubation of 5 min after remifentanil and 4 min after fentanyl.[1] However, seven of 31 patients who received fentanyl required naloxone and in two the trachea was still intubated at 1 h because of "excessive somnolence". The design of this study was unusual with isoflurane reserved for patients showing persistent haemodynamic responses not responsive to additional opioid and the majority of patients received only nitrous oxide as a hypnotic. In addition, the double-blind design required that the first three haemodynamic responses were treated with bolus injections when the pharmacokinetic profile of remifentanil suggests that an increase in infusion rate would have been more appropriate.

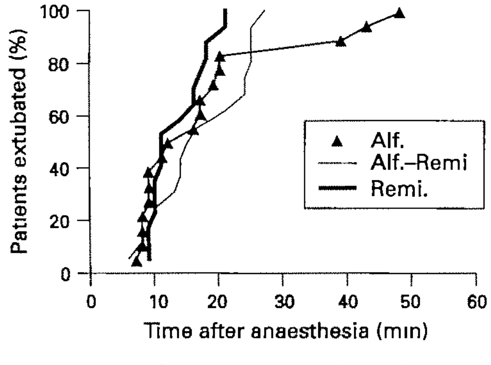

Figure 1 Percentage of patients in whom the trachea was extubated in the first hour after anaesthesia in group Alf. (alfentanil 50 µg kg^{-1} followed by 0.833 µg kg^{-1} min^{-1} until dural closure), group Alf.–Remi. (alfentanil 50 µg kg^{-1} followed by 0.833 µg kg^{-1} min^{-1} for 2 h, then remifentanil 0.25 µg kg^{-1} min^{-1}) and group Remi (remifentanil 1 µg kg^{-1} followed by 0.5 µg kg^{-1} min^{-1} reducing to 0.25 µg kg^{-1} min^{-1} after craniotomy). Recovery times are in minutes from termination of anaesthesia.

In our study, we considered carefully the feasibility of a double-blind treble dummy design but felt that considerations of patient safety and opportunities for error in drug administration made this inappropriate. The majority of clinical studies with remifentanil have used an open design and this seemed sensible for this study. The design of our study imposed a rigid procedure for management of haemodynamic responses and hypotension, and the end-points were relatively clearly defined, thereby limiting the influence of possible investigator bias.

In the absence of pilot data, we were unable to conduct an *a priori* power calculation for this study. *Post hoc* calculations suggest that the study had a power of 54% to detect a 50% reduction in the time to extubation between two groups at a two-sided 5% significance level. To achieve a power of 80% would have required a total of 150 patients.

When designing the study we considered the use of target-controlled infusion systems to deliver propofol and the opioids, but such systems are not approved for use with opioids and their use would have reduced the relevance of our findings to clinicians without access to such equipment. We have simulated the alfentanil and remifentanil infusions during the first 120 min of anaesthesia using the pharmacokinetic modelling and drug infusion software Stanpump (version June 13 1995) (fig. 2). (Stanpump is freely available from Steven L. Shafer, MD, Anesthesiology Service (112A), PAVAMC, 3801 Miranda Avenue, Palo Alto, CA 94304, USA and on the world wide web at http://pkpd.icon.palo-alto.va.gov.) It is clear

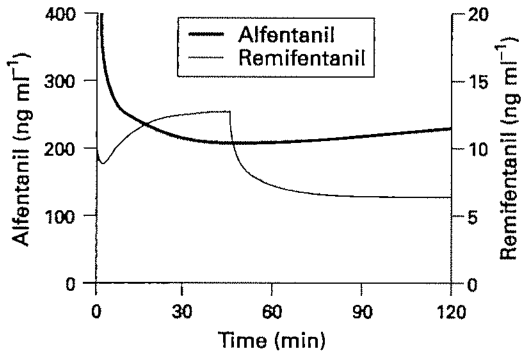

Figure 2 Pharmacokinetic simulations showing predicted plasma concentrations of alfentanil and remifentanil during the first 2 h of infusion. Note that remifentanil was reduced from 0.5 to 0.25 μg kg^{-1} min^{-1} at 45 min as this is approximately when drilling was ceased in a typical case.

from these simulations that the predicted plasma concentration of alfentanil is relatively stable during the first 2 h and that the relative concentrations of the two opioids are not grossly dissimilar when allowance is made for their potency ratio (we have used 20:1 although it could be higher or lower as published ratios range from 8:1 to 58:1).[5,6]

All of our patients received an infusion of opioid and, in this context, administration of nitrous oxide may have been unnecessary. Nitrous oxide was included in the anaesthetic because we were unfamiliar with the use of remifentanil in neuroanaesthesia and wished to ensure adequate hypnosis. In addition, a lower dose of propofol might have been adequate as both alfentanil and remifentanil have been shown to reduce propofol requirements for clinical anaesthesia.[7,8] These factors may have contributed to the relatively prolonged recovery times in all three groups. We chose doses of alfentanil and remifentanil which are in line with the recommendations of the manufacturers. Nevertheless, inter-patient pharmacokinetic variability and accumulation of alfentanil may also have contributed to the delayed recovery of three patients in group Alf.

Our alfentanil infusion scheme was based on previous experience with this drug. The remifentanil scheme used in group Remi. followed published doses.[9] A reduction in remifentanil dose has been recommended for elderly patients,[10,11] however, our study made no allowance for age. In group Remi., all three patients aged more than 65 yr had one or more episodes of hypotension as did 10 of 14 aged less than 65 yr. However, these numbers are too small to draw meaningful conclusions.

This was not a health economic investigation, however; using the current costs to our institution (remifentanil £5.50 for 1 mg and alfentanil £0.72 for 1 mg) and costing these agents in whole multiples of these amounts, the median opioid costs were: group Alf. £10.08, group Alf.–Remi. £18.24 and group Remi. £22.20. These costings make no allowance for the additional syringe and tubing used in group Alf.–Remi. Propofol cost £4.44 for 200 mg and the median propofol costs of the three groups were: group Alf. £35.80, group Alf.–Remi. £38.50 and group Remi. £33.00. Overall median costs of propofol with opioid were: group Alf. £47.86, group Alf.–Remi. £56.74 and group Remi. £55.20. Thus when used in combination with nitrous oxide and propofol, sequential treatment with alfentanil followed by remifentanil was more expensive than using remifentanil alone and did not confer any clinical advantage.

Our study was relatively small and should be interpreted cautiously. Although intraoperative conditions were generally satisfactory with improved haemodynamic stability in group Remi., recovery times may reflect excessive hypnosis and suggest that further improvements may be possible. Future investigations might usefully compare remifentanil and alfentanil, and possibly a sequential opioid infusion design without nitrous oxide and with a lower dose of propofol.

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Patient-maintained remifentanil target-controlled infusion for the transition to early postoperative analgesia

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Summary

We studied 30 male patients in the early postoperative period to assess the efficacy, safety and feasibility of a patient-demand, target-controlled infusion (TCI) of remifentanil. All patients received the same TCI-based propofol–remifentanil anaesthetic for elective orthopaedic surgery. At the end of surgery, infusion of remifentanil was reduced progressively until patients were breathing spontaneously. After extubation and transfer to the post-anaesthesia care unit, patients were given control of a handset and were able to increase the target remifentanil blood concentration by increments of 0.2 ng ml^{-1}. If there were no demands, the TCI controller automatically reduced the target concentration. Pain scores, sedation level, ventilatory frequency, oxygen saturation and nausea were assessed. Mean time to onset of satisfactory analgesia (VAS $\leq$3, out of 10) was 18.9 (95% confidence interval (CI) 15.8–21.9) min at a mean target remifentanil concentration of 2.02 (CI 1.87–2.16) ng ml^{-1}. There were no episodes of hypoxaemia and the lowest ventilatory frequency was 9 bpm. Nausea occurred in 26.6% of patients and 10% vomited. The majority of patients were only slightly sedated. These results imply an effective tool without respiratory side effects in the early postoperative period after anaesthesia using remifentanil as the analgesic component. (*Br. J. Anaesth.* 1998; **81**: 365–368).

Keywords: analgesia, patient-controlled; analgesic techniques, infusion; analgesics opioid, remifentanil; pain, postoperative

Remifentanil is a novel, short-acting μ receptor opioid agonist, which has been introduced recently into clinical anaesthetic practice in most European countries and the USA. Its unique metabolism offers a favourable pharmacokinetic profile which results in rapid offset of drug effect, even after long infusions, expressed as a context-sensitive half-time of approximately 3 min, regardless of the duration of infusion.[1] These properties should confer ease of titration for changing intraoperative conditions. However, a major disadvantage of remifentanil is the appropriate transition to postoperative pain control, as the rapid offset of action has been shown to produce inadequate immediate postoperative analgesia,[2] which may adversely affect patient recovery and outcome.

In contrast, alfentanil, whose context-sensitive half-time is duration-dependent, has been shown to provide good quality analgesia after major surgery when administered as a target-controlled infusion (TCI) based on a three-compartment pharmacokinetic model.[3] In this study we have assessed the efficacy, safety and feasibility of a patient-demand TCI for remifentanil for the transition to the early postoperative phase.

Patients and methods

After obtaining approval from the Institutional Ethics Committee and written informed consent, we studied 30 consecutive male patients, ASA I and II, undergoing elective orthopaedic surgery. These procedures (table 1) have been shown to produce moderate to severe postoperative pain with comparable analgesic requirements at our institution. Patients older than 65 yr or with a known history of chronic drug or alcohol abuse were excluded, as were those suffering from obesity, expressed as a body mass index >30 kg (m^2)$^{-1}$. During the pre-anaesthetic visit, patients were instructed in the principles of patient-controlled analgesia (PCA) and after arrival at the preoperative preparation area the use of a PCA handset was demonstrated.

The anaesthetic technique was standardized. After premedication with oral clorazepate dipotassium 0.25 mg kg^{-1}, 1 h before surgery, anaesthesia was induced and maintained with 1% propofol and remifentanil 1 mg/50 ml (20 μg ml^{-1}) using TCI. TCI systems are designed to rapidly achieve and maintain predefined drug concentrations based on microcomputer-generated pharmacokinetic algorithms.[4] They were programmed with pooled pharmacokinetic data for propofol[5] and remifentanil[6] and adjusted for patient age and weight. The TCI controller, which contains the microcomputer and a display showing the calculated target plasma and effect site concentrations, was connected via a serial link to a Graseby 3400 syringe pump (Graseby Medical Inc., Watford, UK) to administer the anaesthetic drug. Beginning with a target concentration of 2.5 μg ml^{-1}, propofol TCI was titrated until loss of consciousness, expressed as a loss of response to verbal commands and loss of the eyelash reflex (C_{PT}=target plasma con-

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Table 1 Orthopaedic procedures (n=30)

Procedure	n
Arthroscopic knee joint surgery (not diagnostic)	7
Open repair of anterior cruciate ligament	9
Partial knee replacement	9
Shoulder arthroscopy and surgery	3
Fracture of the talus	2

centration; nomenclature according to Glass and colleagues).[7] Thereafter, remifentanil TCI was started to achieve an initial C_{PT} of 4 ng ml^{-1}. Neuromuscular block was facilitated with vecuronium 0.1 mg kg^{-1}, the trachea was intubated and the lungs ventilated with 70% nitrous oxide in oxygen. Vecuronium was given only for tracheal intubation, and recovery of neuromuscular block was monitored by train-of-four counts. No antagonism of drug was necessary. End-tidal carbon dioxide tension was kept in the normocapnic range (4.6–5.8 kPa). Respiratory and cardiovascular monitoring were performed according to our institution's standard practice and consisted of electrocardiogram, non-invasive arterial pressure and pulse oximetry. For maintenance of anaesthesia, propofol TCI was continued at the induction target at which unconsciousness occurred, while the remifentanil target was increased in steps of 0.5 ng ml^{-1} when signs of inadequate anaesthesia developed. This was defined by one or more of the following criteria: increase in systolic arterial pressure by more than 20 mm Hg above pre-intubation values; heart rate greater than 90 beat min^{-1} in the absence of hypovolaemia; autonomic signs, such as sweating or flushing; and somatic responses, such as movement, swallowing or coughing.

Approximately 10 min before the anticipated end of surgery, infusion of propofol was stopped and the target concentration of remifentanil was reduced progressively in decrements of 0.1 ng ml^{-1} until patients were breathing spontaneously at a ventilatory frequency of ≥10 bpm. The target concentration of remifentanil at which each individual patient regained consciousness and tracheal extubation occurred was maintained until they were transferred to the post-anaesthesia care unit (PACU). A handset was connected to the TCI controller and the patient was given control. By pushing the demand button twice within 1 s when pain relief was required, the patient was able to increase the target concentration of remifentanil. The target concentration of remifentanil was increased by 0.2 ng ml^{-1} after every successful demand. We chose a double push for every demand to ensure a minimum of alertness of the patient. There was a lockout time of 2 min after each increase in target concentration. In the absence of a demand within a 30-min period, the target concentration was automatically reduced by 0.2 ng ml^{-1} during the first 4 h and further reductions of 0.2 ng ml^{-1} were made every 45 min during the following 4 h.

After arrival in the PACU all patients were observed for the next 6 h and ventilatory frequency, oxygen saturation, pain and level of sedation were monitored. No additional oxygen was given unless Sa_{O_2} decreased to less than 95%. Assessments and observations started with initiation of the handset controller and were made every 3 min until adequate analgesia was provided and every 15 min thereafter. Pain on movement was assessed using an 11-point (0–10) visual analogue scale (VAS) with 0=no pain and 10=worst pain imaginable. Patient rating scores of 3 or less were defined as adequate analgesia. The degree of sedation was recorded using the six-point scale described by Ramsay and colleagues.[8] Every episode of nausea or vomiting was documented. After matching the "adequate analgesia" criteria (VAS ≤3), rectal diclofenac 100 mg was administered for further analgesia to every patient, except those with underlying renal impairment or a history of gastric ulcer. Remifentanil TCI was terminated after the observation period of 6 h by tapering off the infusion within 15–20 min. I.v. piritramide or standard morphine PCA was prescribed in patients with additional analgesic requirements.

STATISTICAL ANALYSIS

Data are presented as mean, absolute range and 95% confidence intervals (CI). Patient values are given as mean (SEM). The relationships between target remifentanil concentration and ventilatory frequency and sedation score were investigated using regression analysis. Student's t test was used to compare target remifentanil concentrations for spontaneous ventilation and adequate analgesia, with $P<0.05$ considered significant. All analyses were performed using the StatView statistical software package (v.4.5, Abacus Concepts, Berkeley, CA, USA).

Results

A total of 30 patients, mean age 41.6 (range 18–65) yr and mean weight 72 kg (SEM 1.9) were included. Mean duration of surgery was 2.07 (SEM 0.12) h. The remifentanil TCI system functioned well and there were no technical problems during the study. Patients found it easy to use the handset and were satisfied with the PCA device. At the end of surgery, infusion of propofol was stopped at 4.2 (95% CI 2.2–5.1 CI) μg ml^{-1} and the reduction in TCI remifentanil started with 4.8 (4.2–5.5) ng ml^{-1}. The mean target remifentanil concentration at which spontaneous ventilation was first noted after the end of surgery was 1.05 (0.97–1.14) ng ml^{-1}, significantly less ($P<0.0001$) than that required for adequate analgesia after operation, which was 2.02 (1.87–2.16) ng ml^{-1}. The variation between patients for these values was more than 200% (table 2). In contrast, the mean residual calculated target propofol concentration at the time of spontaneous ventilation was 1.2 (0.9–1.8) μg ml^{-1}.

Mean time to adequate analgesia (VAS ≤ 3) was 18.9 (15.89–21.91) min. With two exceptions, every patient achieved adequate analgesia within 30 min. There were no episodes of hypoxaemia (oxygen saturation <95%) or apnoea, and the lowest ventilatory frequency was 9 bpm (table 3). The majority of patients were only slightly sedated (median sedation score 2, out of a possible 6). The target concentration of remifentanil showed a linear correlation with slowing of ventilatory frequency ($r^2=-0.7$) and level of sedation. The frequency of nausea and vomiting was 26.6% and 10%, respectively, and occurred predominantly in patients with relatively high and rapid increases in target concentrations of remifentanil.

Table 2 Target remifentanil concentration (C_{PT}) ng ml^{-1} for sufficient spontaneous ventilation (TC $_{sv}$) and adequate postoperative analgesia (TC$_{VAS<3}$), in addition to time for adequate postoperative analgesia (VAS<3) (mean, range of absolute values and 95% confidence interval (CI))

		CI variance	
	Mean (range)	95% lower	95% upper
TC $_{SV}$ (ng ml^{-1})	1.03 (0.6–1.6)	0.76	1 48
TC $_{VAS<3}$ (ng ml^{-1})	2.02 (1.2–2.8)	1.43	2 69
VAS<3 (min)	18.9 (8–45)	10.2	28.5

Table 3 Ventilatory frequency and oxygen saturation at the time of adequate analgesia (VAS≤3) (mean, range of absolute values and 95% confidence interval (CI))

		CI variance	
	Mean (range)	95% lower	95% upper
Ventilatory frequency (bpm)	16.5 (9–23)	14.9	18.1
Oxygen saturation (%)	98.2 (95–100)	97 5	98.8

Moderate postoperative shivering occurred in two patients but required no treatment.

Discussion

In this study, we have demonstrated that in 30 patients, infusion of remifentanil maintained by patient-controlled TCI was an effective and safe postoperative analgesic technique in the early period after remifentanil–propofol anaesthesia.

To overcome the disadvantage of immediate painful conditions after stopping infusion of remifentanil, which occurs significantly earlier compared with other opioids,[9] several studies examined the feasibility of a manually controlled remifentanil infusion. Bowdle and co-workers compared different infusion rates (0.05–0.15 μg kg^{-1} min^{-1}) and the effect of incremental bolus doses in a multicentre study.[10] They found adequate analgesia in 78% of patients within 30 min, but adverse respiratory effects were a notable problem (29% of patients, 7% apnoea). In another multicentre study comparing remifentanil with alfentanil for major abdominal surgery, Schüttler and colleagues titrated a manual infusion beginning with 0.1 μg kg^{-1} min^{-1}.[11] They found that rapid changes in remifentanil blood concentration by bolus administrations or increases in infusion rate resulted in a high frequency of muscle rigidity, respiratory depression and apnoea. An editorial comment to this article stated that using remifentanil in the manner described was unacceptable.[12] Similar results were reported recently by Yarmush and co-workers.[13] They conducted a double-blind comparison of manually controlled remifentanil infusion (median rate 0.125 μg kg^{-1} min^{-1}) with morphine boluses during the first 25 min after the end of surgery. Transient respiratory depression, apnoea or both (14%) were the most frequent adverse effects in the remifentanil group. The incidence of nausea and vomiting seemed to be highly variable in these studies. There was no significant difference in the frequency of vomiting in our study compared with that of Bowdle and colleagues (approximately 10%), but Schüttler and co-workers reported that 47% of patients in the remifentanil group suffered nausea, which is almost twice that seen in our patients (26%). In contrast, the study of Yarmush and colleagues described an incidence of 17% nausea in the remifentanil group compared with 6% in the morphine group. This suggests a dose-dependent adverse effect which may be aggravated by incremental manual bolus doses.

A theoretical advantage of remifentanil TCI, which increases the blood concentration by a controlled stepwise titration of only small boluses, is the avoidance of an uncontrolled overshoot in blood concentration associated with manual bolus administration. As remifentanil has a fast effect site equlibration ($T_{1/2}$ k_{e0}=1.6 min),[14] every new target results in rapid onset and rapid achievement of a stable level of drug effect. In fact, none of our patients experienced significant respiratory depression, and sufficient analgesia was achieved in a reasonable time.

Alfentanil, which has a comparable effect site equilibration to remifentanil, has been shown by van den Nieuwenhuyzen and colleagues to be significantly faster in onset of analgesia compared with morphine when used as TCI.[15] With a mean time of 20 min from the start of therapy to onset of sufficient analgesia, their results were similar to our finding of 18 min with remifentanil. Similar results have been reported by Irwin and co-workers using patient-controlled alfentanil TCI, which was as safe and effective as standard morphine PCA after orthopaedic surgery.[16]

Our finding, that the mean remifentanil target concentration for recovery of spontaneous ventilation at the end of surgery was approximately 50% of that for adequate pain control thereafter, was probably because of a residual anaesthetic effect of propofol and reflects a possible pharmacodynamic interaction of the two drugs.

We did not measure remifentanil blood concentrations and therefore we could not estimate the performance of the remifentanil TCI. However, the pharmacokinetic data used to programme the TCI controller have been shown to be sufficiently reliable. Pharmacokinetic bias and precision, expressed as relative and absolute percent performance error, are reported to be 26% and 19% respectively,[6] which are comparable with data obtained for alfentanil and sufentanil TCI–PCA .[17] Even if we knew the actual blood concentrations of remifentanil, this would be only a minor contribution as the pharmacodynamic variance of the required target concentrations between individual patients (approximately 200%) exceeds the expected pharmacokinetic error.

Another possible source of inaccuracy could be the physical performance of the infusion pump and dilution of the drug. A remifentanil concentration of 50 μg ml^{-1} has been reported to be associated with a high incidence of opioid-induced adverse effects when used as a manual infusion.[10] The choice of i.v. tubing, deadspace of taps or three-way valves, and changes in flow rates of additional fluids may substantially influence moment-to-moment delivery, resulting in varying drug concentrations. Therefore, we used a low concentration of remifentanil (20 μg ml^{-1}) which was connected to the proximal port of the i.v. cannula, flushed by a constant infusion of Ringer's lactate. Even taking these precautions into account, our preliminary experience does not yet support the use of this system without adequate supervision and monitoring.

We conclude that patient-demand target-controlled infusion of remifentanil was a convenient and effective tool for the transition to sufficient analgesia in the early postoperative period. As our preliminary experience was limited to 30 patients, the safety of the system and lack of respiratory side effects have to be discussed with caution. To validate this technique against standard PCA bolus therapy, further controlled studies are needed.

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Ketorolac, diclofenac and ketoprofen are equally efficacious for pain relief after total hip replacement surgery

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Summary

We have compared the efficacy of ketorolac 30 mg i.v. followed by infusion at a rate of 90 mg/15.5 h, with that of diclofenac 75 mg followed by infusion of 75 mg/15.5 h or ketoprofen 100 mg followed by infusion of 100 mg/15.5 h, on postoperative pain in 85 patients after hip replacement surgery under spinal anaesthesia in a prospective, double-blind, randomized study. Supplementary analgesia was administered during the 16-h postoperative period with bolus doses of fentanyl delivered by a patient-controlled analgesia system. Mean total consumption of PCA-administered fentanyl was 890 (SD 400) μg in the ketorolac group, 920 (550) μg in the diclofenac group and 850 (350) μg in the ketoprofen group (ns). Median VAS scores were low over the entire study in each group and there was no significant difference between groups. No serious adverse events were recorded. (*Br. J. Anaesth.* 1998; **81**: 369–372).

Keywords: analgesia, patient-controlled; non-steroidal anti-inflammatory drugs; analgesics non-opioid, diclofenac; analgesics non-opioid, ketoprofen; analgesics non-opioid, ketorolac; pain, postoperative

Non-steroidal anti-inflammatory drugs (NSAID) have become popular for pain relief after orthopaedic surgery and their efficacy has been demonstrated in comparison with placebo.[1–3] NSAID reduce the biosynthesis of prostaglandins by inhibition of the enzyme cyclo-oxygenase (COX).[4] This enzyme exists in two different isoforms (COX-1 and COX-2) and NSAID may differ in their inhibition of both COX-I and COX-2 isoenzymes.[5]

Ketorolac inhibits both cyclo-oxygenase and lipo-oxygenase enzymes thereby preventing the synthesis of both prostaglandins and leukotrienes,[6] and may also release endogenous opioids.[7] These properties of ketorolac may make it more potent than other NSAID. For example, ketorolac 30 mg i.m. has been shown to be as effective as morphine 12 mg i.m. or meperidine 100 mg i.m. for severe pain after major surgery.[8]

Although there are many studies comparing NSAID with placebo and opioids, there are few comparisons between NSAID after major surgery. The analgesic efficacy of ketorolac was greater than that of diclofenac after arthroscopy of the knee joint.[9] Niemi, Tuominen and Rosenberg have shown that pain after maxillofacial surgery was reduced more effectively by parenterally administered diclofenac than by parenteral ketoprofen.[10] We investigated if ketorolac offers any advantage over diclofenac or ketoprofen in terms of efficacy of pain relief after hip replacement.

Patients and methods

The study was conducted in accordance with the declaration of Helsinki. After obtaining approval from the Ethics Committee of Kuopio University Hospital and Lappi Central Hospital, and informed written consent, we studied 85 ASA I–III patients, aged 45–81 yr, undergoing total hip replacement surgery, in a double-blind, randomized, comparative study. Patients with hypersensitivity to anti-inflammatory drugs, asthma, clinical hepatic or renal failure, bleeding or coagulation disorders, gastrointestinal ulceration or dyspepsia were excluded. The use of a visual analogue scale (VAS) was explained to the patients during the preoperative visit.

Patients received diazepam 10–15 mg orally as premedication, 40–60 min before the start of spinal anaesthesia. Isobaric 0.5% bupivacaine 15–20 mg was administered spinally at the L2–3 or L3–4 interspace. No NSAID were given during operation.

The study began after operation in the recovery room (Kuopio) or in the intensive care unit (Rovaniemi) when spinal anaesthesia had worn off at the operation site. This was indicated by pinprick response: the patient was able to detect a sharp pinprick (22-gauge needle) at the operation site. Patients were allocated randomly to receive, in a double-blind manner, diclofenac 75 mg, ketoprofen 100 mg or ketorolac 30 mg as an i.v. loading dose for 30 min, followed by infusion of diclofenac 75 mg, ketoprofen 100 mg or ketorolac 90 mg over 15.5 h. A 16-h period was chosen because we were unable to keep the patients in the recovery room or in the intensive care unit for a longer time. A nurse not involved in the study prepared all drugs according to the randomization, in the form of sealed envelopes.

Patients were given access to a patient-controlled analgesia pump (PCA) (Graseby PCAS, Medical Ltd, Watford, Herts, UK) which was programmed to

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deliver on demand fentanyl 50 µg i.v.: infusion time was 5 min, lock-out time was 5 min and maximum dose was 300 µg h^{-1}. Patients were instructed to administer fentanyl whenever they required pain relief, and all successful and unsuccessful demands were recorded.

Pain intensity at rest was assessed using a 10-cm linear VAS (0=no pain, 10=worst pain imaginable). Patients undergoing total hip replacement are not usually mobile during the first 24 h, so pain intensity was assessed only at rest. The first postoperative pain score was obtained before the i.v. loading dose, the next score at the end of the loading dose and then at 3, 6, 10, 13 and 16 h after the beginning of the study. Pain at the infusion site during infusion of the loading dose was noted.

Sedation was recorded at the same intervals by nurses (0=completely alert, 1=dozes now and then, but answers immediately, 2=asleep often, but rousable, 3=asleep and not rousable).

Ventilatory frequency, oxygen saturation, arterial pressure, heart rate, nausea, vomiting and itching (yes=1/no=2) were measured at the same intervals as pain intensity. During the assessment, nurses also recorded the lowest oxygen saturation. Patients were given supplementary oxygen 2 litre min^{-1} if oxygen saturation was less than 90%. Postoperative blood loss was determined by measuring the contents of the suction bottles at the beginning and end of the study. Blood loss was replaced with infusions of Ringer's acetate and hydroxy ethyl starch. Packed red cells were given if needed to maintain a haemoglobin concentration greater than 100 g $litre^{-1}$.

The sample size was estimated to demonstrate with 90% power and at the 5% significance level[11] a difference of 30% in fentanyl consumption. The chi-square test was used to study the homogeneity of the groups in terms of sex, ASA classification and incidence of adverse effects. Analysis of variance with repeated measures was used for VAS scores. One-way analysis of variance was used for the rest of the variables and Scheffe's test to locate the differences. The homogeneity of variances was tested with Levene's test. The level of statistical significance was set as $P<0.05$.

Results

All 85 patients completed the 16-h study: 28 patients in the diclofenac group, 29 in the ketoprofen group and 28 in the ketorolac group. Patients who received diclofenac were significantly younger than those who received ketoprofen ($P=0.02$), while the difference between the diclofenac and ketorolac groups was not significant. There were no differences in sex, weight, ASA class, duration of operation, perioperative blood loss, postoperative drainage volume or duration of spinal anaesthesia between the groups (table 1).

There was no significant difference in mean total consumption of PCA-administered fentanyl between the three groups during the 16-h study: 890 (SD 400) µg in the ketorolac group, 920 (550) µg in the diclofenac group and 850 (350) µg in the ketoprofen group. The mean number of unsuccessful attempts from the PCA pump were 6.1 (range 0–41) in the ketorolac group, 5.0 (0–48) in the diclofenac group and 6.3 (0–49) in the ketoprofen group. Eight patients in the ketorolac group, 12 in the diclofenac group and seven in the ketoprofen group had no unsuccessful attempts. The range of unsuccessful attempts was too large to permit application of statistical methods. There were no differences between the groups in mean fentanyl consumption during the 5–6-h observation periods (table 2).

Table 1 Patient characteristics and operation details (mean (SD or range) or number). *P=0 02 compared with diclofenac

	Ketorolac (n=28)	Diclofenac (n=28)	Ketoprofen (n=29)
Age (yr)	65 (54–80)	60 (45–77)	66 (51–81)*
Weight (kg)	77 (12)	79 (20)	75 (10)
Sex (M/F)	16/12	15/13	14/15
Duration of surgery (min)	108 (25)	109 (28)	106 (19)
Periop. blood loss (ml)	782 (331)	917 (662)	897 (495)
Duration of anaesthesia (min)	254 (55)	245 (44)	250 (52)
Drainage volume (ml)	795 (466)	725 (389)	798 (614)

Table 2 Mean (SD) [range] fentanyl consumption (µg h^{-1}) during the 16-h study. No significant differences

Time	Ketorolac	Diclofenac	Ketoprofen
0–5 h	60 (40) [10–150]	60 (30) [0–110]	70 (40) [10–150]
5–10 h	50 (40) [20–130]	50 (30) [0–130]	70 (40) [0–170]
10–16 h	50 (30) [20–110]	40 (30) [10–150]	50 (20) [10–100]
0–16 h	890 (400)	920 (550)	850 (350)

Median VAS scores were low over the entire study and there was no significant difference between groups (fig. 1).

There were no significant differences between groups in level of sedation, ventilatory frequency, heart rate, arterial pressure or oxygen saturation. Seven patients in the diclofenac group, 10 in the ketoprofen group and 12 in the ketorolac group required supplementary oxygen. Median oxygen saturations were 95–97% in all groups during the study.

The incidence of adverse effects is presented in table 3. Four patients in the diclofenac group and three in the ketoprofen group complained of pain or discomfort at the injection site compared with only one patient in the ketorolac group. However, there were no significant differences between groups.

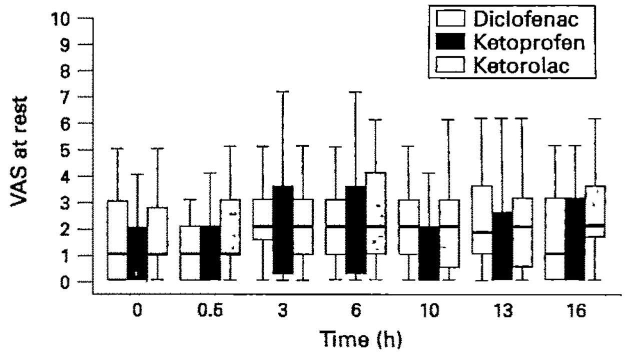

Figure 1 Pain at rest in the diclofenac, ketoprofen and ketorolac groups, expressed as visual analogue scale (VAS) scores. The box represents the 25–75th percentiles and the median is represented by the solid line. Lines are drawn from the end of the box to the largest and smallest observed values that are not outliers. No significant difference between groups.

Table 3 Adverse effects experienced in the three groups. No significant differences

Adverse effect	Ketorolac (n=28)	Diclofenac (n=28)	Ketoprofen (n=29)
Nausea	9	9	10
Vomiting	9	5	8
Itching	4	3	1
Pain at infusion site	1	4	3

Discussion

We found that ketorolac was equally efficacious as diclofenac and ketoprofen for the treatment of postoperative pain after hip replacement surgery. There were no significant differences between groups in mean total consumption of fentanyl during the 16-h study or in mean fentanyl consumption when measured in 5–6-h periods. Median VAS scores were low in all groups with no significant differences between groups. Adverse effects were minor, mostly nausea and vomiting, and were similar in the three groups.

The doses of anti-inflammatory drugs used in this study were based on the recommended maximal daily doses provided by the manufacturers. We considered the use of a placebo group to be unnecessary as the opioid-sparing effect of diclofenac and ketoprofen compared with placebo after similar surgery in similar patients had been demonstrated in previous studies from our departments.[1 2] In our ketoprofen study we compared the analgesic efficacy of i.v. ketoprofen 100 mg/12 h, 200 mg/12h and 300 mg/12h with a placebo group after total hip or knee replacement.[2] Total consumption of fentanyl during the study, used as rescue analgesia delivered by PCA, was significantly lower in all ketoprofen groups compared with placebo. Laitinen and Nuutinen compared i.v. diclofenac 150 mg/16 h with placebo after total hip replacement and in this study the diclofenac group showed a significant reduction in the amount of fentanyl administered during the 16-h study compared with the placebo group.[1]

NSAID have potential side effects on platelet and renal function. There is always a risk of major haemorrhage, hypovolaemia and thereby renal underperfusion after hip replacement surgery. Administration of NSAID in the hypovolaemic situation may lead to severe renal failure, especially in older age groups. The short-term use of NSAID for surgical patients does not seem to induce irreversible renal failure, however, prospective controlled studies with large populations are required to study the incidence of renal side effects after administration of NSAID. NSAID inhibit platelet aggregation as long as they remain in the blood stream.[12] There have been controversial results regarding postoperative bleeding with parenteral ketorolac.[13 14] Strom and co-workers reported a low risk of operative site bleeding with ketorolac,[13] Gallagher, Blauth and Fornadley demonstrated an approximately five-fold increase in postoperative haemorrhage in patients who had received ketorolac in the perioperative period for tonsillectomy and adenoidectomy.[14] Niemi, Taxell and Rosenberg compared the effect of i.v. ketoprofen 1.4 mg kg^{-1}, ketorolac 0.4 mg kg^{-1} and diclofenac 1.1 mg kg^{-1} on platelet function in 10 healthy volunteers.[15] The drugs were administered on three different occasions, at more than 1-week intervals, in a randomized, double-blind, crossover study. Ketoprofen, ketorolac and diclofenac caused reversible platelet dysfunction. Diclofenac had the mildest effect, while platelet dysfunction was still seen 24 h after administration of ketorolac. In our study, we measured drainage volumes from the operation site during the study and there was no clinical or significant difference between groups.

In our study, all anti-inflammatory drugs were administered i.v. when spinal anaesthesia began to wear off at the operation site. Median VAS scores were the same (1.0) in all groups at the beginning of the study. The low VAS scores were probably a result of the use of the PCA device. However, there were patients in every group who had periodic short-term demands which were not covered by the PCA settings. All patients using a PCA device suffer a short period of inadequately relieved pain. With PCA, patients first have pain and then press the button, and there is a delay between administration of an analgesic and its action. However, the amount of analgesic delivered via the PCA device is an objective method for assessment of the efficacy of postoperative pain therapy.

Morrow, Bunting and Milligan compared the analgesic efficacy and side effects of ketorolac with diclofenac after day-case arthroscopy of the knee joint.[9] They administered a single deep i.m. injection of either ketorolac 30 mg or diclofenac 75 mg. Ketorolac provided better postoperative analgesia compared with diclofenac, was associated with a low incidence of pain at the injection site and the authors suggested that the superiority of ketorolac was underestimated. Morley-Forster, Newton and Cook compared i.m. ketorolac, rectal indomethacin and a placebo in healthy women undergoing gynaecological or breast surgery as outpatients.[16] The NSAID-treated groups had less pain and required less fentanyl than the placebo group, but there were no differences between the two NSAID. Rorarius and co-workers compared the effect of constant infusion of diclofenac at a rate of 150 mg/24 h and ketoprofen 200 mg/24 h for the treatment of postoperative pain after elective Caesarean section and found these doses to be of similar efficacy.[17]

In summary, we have found that ketorolac was as efficacious as diclofenac and ketoprofen in the treatment of postoperative pain after hip replacement surgery.

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British Journal of Anaesthesia 1998; **81**: 373–376

Influence of timing of morphine administration on postoperative pain and analgesic consumption

A. Y. MILLAR, M. D. MANSFIELD AND J. KINSELLA

Summary

We have investigated if a pre-emptive dose of morphine, given 30 min before skin incision, influenced postoperative pain and morphine consumption after hysterectomy. In a prospective, randomized, double-blind, placebo-controlled clinical study, patients received morphine 0.3 mg kg^{-1} at induction of anaesthesia or 30 min later at skin incision. The primary endpoint was defined as 24-h morphine consumption via patient-controlled analgesia. We could not demonstrate any difference between the two groups in morphine consumption or pain scores, and we conclude that there was no evidence of pre-emptive analgesia in this study. (*Br. J. Anaesth.* 1998; **81**: 373–376)

Keywords: analgesics opioid, morphine; analgesia, pre-emptive; analgesia, patient-controlled, pain, postoperative

There has been some interest in the concept of pre-emptive analgesia since it was first proposed[1] because of the suggestion that it provides better analgesia, reduced postoperative opioid use and therefore a lower incidence of side effects. The relevance and clinical value of pre-emptive analgesia has been called into question in several reviews.[2,3] Two reports in the anaesthetic literature suggest a clinically significant reduction in postoperative opioid use.[4,5] These reports suggest that postoperative morphine consumption is reduced when peroperative morphine is given at the start of operation compared with at the end. In response to these data, we have designed a study to see if a similar reduction in postoperative morphine requirements can be achieved by giving morphine 30 min before surgery compared with at the start of surgery.

Patients and methods

After obtaining approval from the Institutional Ethics Committee and written informed consent, we studied ASA I or II patients, aged up to 60 yr, undergoing hysterectomy with or without salpingo-oophorectomy. The background to the study was given to patients who were familiarized with the use of visual analogue pain scoring and patient-controlled analgesia (Graseby PCAS). Patients with a history of chronic pain requiring regular use of analgesics, alcohol and drug abusers, and those with a psychiatric history were excluded.

Before starting the study, the hospital pharmacy prepared 75 pairs of ampoules, each pair consisting of one ampoule of morphine 30 mg in 10 ml and the other 10 ml of saline. The pharmacy labelled the ampoules "induction" and "incision" and randomized them so that the investigator did not know if the morphine was given at induction or incision.

Premedicated comprised temazepam 20–30 mg, 1.5 h before operation. Minihep 5000 u. was given s.c at this time. A standardized anaesthetic technique was used consisting of induction with propofol, neuromuscular block with vecuronium 0.1 mg kg^{-1}, and a proportion of the "induction" ampoule (1 ml per 10 kg of body weight, i.e. morphine or saline 0.3 mg kg^{-1}). The trachea was intubated and ventilation controlled artificially with 66% nitrous oxide in oxygen. Anaesthesia was maintained with isoflurane as required.

Droperidol 1 mg was given to prevent nausea and Augmentin 1.2 g used as a prophylactic antibiotic. The contents of the "incision" ampoule (1 ml per 10 kg of body weight, i.e. morphine or saline 0.3 mg kg^{-1}) were given at the start of skin incision in the same manner as with the "induction" ampoule. A period of at least 30 min was rigidly adhered to between induction of anaesthesia and skin incision. No other medication was administered. All surgery was performed via a low transverse suprapubic incision. At the end of the procedure residual neuromuscular block was antagonized with neostigmine and glycopyrrolate, spontaneous respiration was re-established and the patient transferred to the recovery room.

A patient-controlled analgesia device was set to deliver morphine 1 mg as a bolus dose with an interval of 3 min and no background infusion or limits. Anaesthetist-administered bolus doses of morphine were also available in the recovery room at emergence from anaesthesia for those patients with inadequate analgesia. For the next 24 h, patients had access to PCA morphine. No other analgesics were given. At 1, 2, 4 and 24 h, patients were assessed using visual analogue pain scores and verbal rating pain scores both at rest and on movement (deep breath and cough). PCA morphine consumption was noted at these times. At 24 h, the PCA was discontinued and analgesia comprised rectal diclofenac and oral coproxamol. Pain scores were measured again at

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48 h. Nausea and vomiting scores were collected at all of the above times.

Recruitment continued until 60 evaluable patients had been obtained.

STATISTICAL ANALYSIS

From the results of a previous study using similar methodology,[5] we calculated that a power of 0.8 could be obtained, using a significance level of 0.05 and two groups of 30 patients, if a 30% reduction in morphine consumption was to be regarded as a clinically significant result.[6] Analgesic consumption was compared between groups using the Mann–Whitney *U* test. Pain scores were plotted against time. The area under the resultant curves were calculated (AUC 24h) and compared using ANOVA.

All data were collated using an Excel spreadsheet (Microsoft) and statistics were produced using Minitab for Windows (v. 9).

Results

Sixty-eight patients were enrolled in total to achieve 60 evaluable patients. Eight patients were withdrawn (three patients had a vertical midline incision, two were inadvertently given rectal diclofenac on the first postoperative evening, one had a panic attack, one developed respiratory depression 3 h after operation and was given naloxone, and one went back to theatre with intra-abdominal bleeding).

After exclusions, there were 30 patients in each group. Patients were similar in age, weight, delay between induction and incision, and duration of surgery (table 1).

There were no differences between the groups in 24-h morphine use. There were no significant differences in morphine use in the recovery room or at any time thereafter (table 2). Pain scores at the various times were also similar throughout the study (figs 1, 2) and there was no difference in VAS pain scores, expressed as AUC over 24 h (table 3).

Table 1 Patient data and surgical details (mean (range)). No significant differences

	Induction group	Incision group
n	30	30
Age (yr)	38.1 (22–56)	40.4 (29–55)
Weight (kg)	63.5 (47–84)	64.5 (46–85)
Induction–incision delay (min)	32.5 (30–36.75)	33.5 (30–38)
Duration of surgery (min)	50 (40–64.5)	53.5 (41.5–67.75)

Table 2 Cumulative morphine consumption via patient-controlled analgesia. Data are median (interquartile range) morphine consumption (mg). No significant differences (Mann–Whitney *U* test)

	Induction group	Incision group
Recovery room	0 (0–3.75)	0 (0–2)
1 h	3.5 (1–8)	5 (1.25–6)
2 h	7 (3–14.25)	8 (4.24–12.5)
4 h	13 (8.25–22)	12 (9–20.75)
24 h	58 (35.5–74.5)	57.5 (34.5–82.25)

Table 3 Area under the curve (AUC) pain scores. No significant differences

	Mean	SD
AUC 24 h (rest)		
Induction group	991.3	455.6
Incision group	872.0	350.2
AUC 24 h (movement)		
Induction group	1079.5	454.7
Incision group	1042.5	402.8

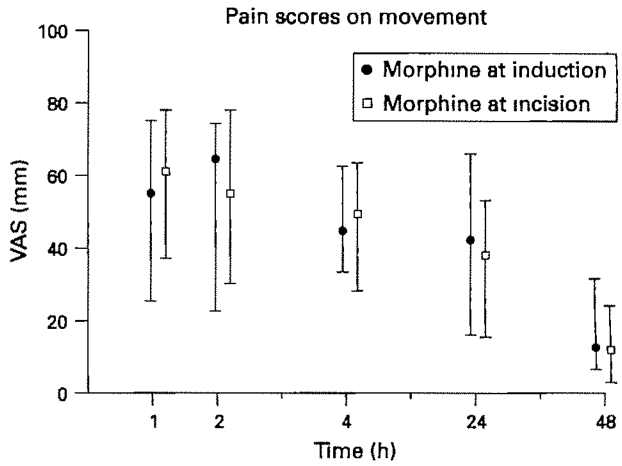

Figure 1 Pain scores, assessed by visual analogue scale (VAS), at 1, 2, 4, 24 and 48 h at rest, in patients who received morphine 0.3 mg kg^{-1} at induction of anaesthesia or 30 min later at skin incision (median and interquartile range).

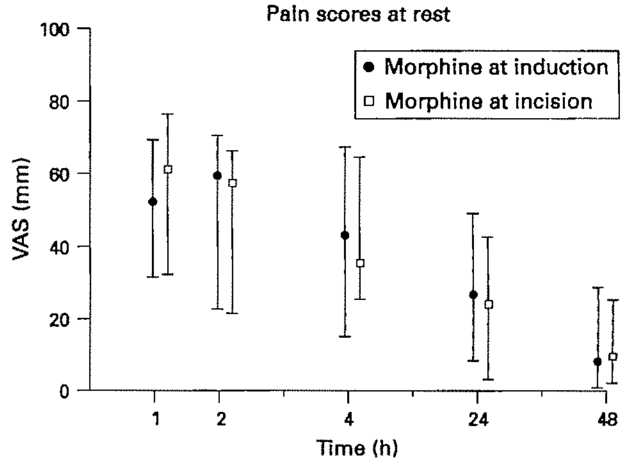

Figure 2 Pain scores, assessed by visual analogue scale (VAS) at 1, 2, 4, 24 and 48 h on movement (deep breath and cough), in patients who received morphine 0.3 mg kg^{-1} at induction of anaesthesia or 30 min later at skin incision (median and interquartile range).

Discussion

Administration of analgesic drugs before a painful stimulus is practised by some in the belief that it reduces postoperative pain. This reduction, if it exists, must occur by one of two mechanisms. Either, administering the analgesic early assures that it is present in sufficient quantity at its effector site or that opioid analgesia given before a painful stimulus somehow modifies the central processing of pain information, reducing spinal cord excitability and thus reducing pain.

The theory that pre-emptive use of opioids can alter spinal cord excitability originates from several experimental observations, largely in animals. After injury, several changes take place both peripherally and centrally in the nervous system that explain the development of pain. Peripherally there is sensitization of nocioceptors[7] in the damaged tissue which leads to an area of primary hyperalgesia at the injured site. In addition, surrounding the injured area is an area of secondary hyperalgesia which may result from changes that occur in the spinal cord,[8] such as increased sensitivity of dorsal horn neurones and expansion of their receptive fields.[9] Both peripheral and central mechanisms contribute to postoperative pain. If these mechanisms could be prevented or obtunded by prior treatment with analgesics, theoretically postoperative pain could be lessened or abolished.

In electrophysiological studies there is a biphasic response in spinal cord dorsal horn activity after peripheral injury.[10] A brief *acute* phase of intense activity related to the injurious stimulus occurs, followed by a delayed but more persistent secondary or *tonic* phase, which is thought to be related to spinal hyperexcitability, central sensitization or "wind-up". An opioid given before a noxious stimulus prevents some of the secondary tonic phase changes that would otherwise develop.[11] Even when the opioid is subsequently antagonized with naloxone, the secondary changes do not occur.[11] Nerve section also creates a biphasic response. It can be shown that both intrathecal and i.v. morphine suppress the secondary tonic phase response to this, although they have minimal influence on the initial acute phase.[12]

On the basis of these observations it is hypothesized that a clinically useful effect may be achieved by pretreating patients with opioids before surgery. The subject was reviewed by Dahl and Kehlet who concluded that further well designed clinical studies were required.[3] There are still only a few clinical studies which prospectively attempted to demonstrate this. The first of these claimed a reduction in postoperative analgesia but the study was poorly controlled and neither randomized nor blinded.[13] The next showed an apparent reduction in postoperative morphine requirements between those patients receiving morphine before operation and those treated at skin closure.[4] This study is the most convincing clinical evidence available for pre-emptive analgesia using opioids but has yet to be reproduced. In this study the range of values obtained for the main outcome variable (24-h morphine consumption via PCA) was extremely narrow and may represent a type 1 error. The same group attempted to produce a larger pre-emptive effect in similar patients by increasing the pre-emptive dose of morphine, but failed to show any reduction in morphine consumption.[14] Another study[5] attempted to reproduce the results of Richmond, Bromley and Woolf[4] and, in addition, examined if a larger dose of morphine given before surgery could achieve a greater effect. This study could not reproduce the results of Richmond, Bromley and Woolf but demonstrated a reduction in postoperative morphine use when a larger dose of morphine was used before surgery compared with a smaller dose after surgery. Two studies have attempted to use alfentanil to produce a pre-emptive effect.[15 16] Neither was able to demonstrate any effect, possibly because either the dose of alfentanil was too small or its effect too brief to adequately prevent wind-up.

In order to truly pre-empt surgical stimulation, analgesia must be given sufficiently early and persist for the duration of the noxious stimulus. Our study attempted to show the influence of morphine 0.3 mg kg^{-1} given before induction compared with the same dose given at surgical incision. We believe that this dose of morphine approaches the maximum that can be used safely for an operation of modest length such as hysterectomy, without excessive risk of respiratory depression. Morphine is poorly lipid soluble and therefore has a delayed onset of action, even when given i.v., compared with more lipid soluble opioids. In order for morphine to be present at mu receptors at the onset of surgery, it needs to be given some time in advance of the surgical incision. In one group, the pre-emptive dose was given i v. 30 min before incision to ensure that sufficient morphine was at the effector sites by the time surgery started. In the other group it was not given until the surgical incision had been made.

We found no differences between the groups and this may be for several reasons. Morphine given at the start of the procedure may have been wearing off towards the end of operation, allowing hyperexcitability of the spinal cord to take place, thereby abolishing any difference between groups. The control group received morphine commensurate with skin incision. Therefore, these subjects were exposed to a short duration of surgery without effective opioid cover. This short exposure to surgery may not have been of sufficient duration to cause hyperexcitability. This would be unlikely as, in the rat spinal cord, changes take place within seconds of a noxious stimulus.

There may be a dose-related ceiling effect which has been exceeded in this study, obliterating any effect. There is some evidence to support this in that the only convincing study showing opioid mediated pre-emptive analgesia[4] used a modest dose of morphine (10 mg) whereas the other studies using larger doses failed to demonstrate this effect.[5 14] Opioid medication is only one possible way in which to modify pain transmission in the spinal cord. Several neurotransmitters and inflammatory mediators are involved in the process.[17] It is perhaps naive to expect that opioids alone could significantly prevent central sensitization. NMDA receptor antagonists, for example, have been shown to prevent central sensitization after injury. It may be that use of these or other compounds either alone or in combination with opioids have a greater effect than opioids alone.

General anaesthesia itself may exert an effect on the normal course of events in the spinal cord during surgery. This could in theory explain the difficulty in producing pre-emptive analgesia in humans. Finally, it may not be possible to demonstrate a pre-emptive effect in a clinical (surgical) setting as painful stimuli are not confined to the intraoperative period but extend from hours to days after surgery. Therefore, spinal cord wind-up/central sensitization of the spinal cord may occur at any point where analgesia is incomplete.

In summary, we have failed to demonstrate any clinical benefit in terms of reduced postoperative analgesic requirements using morphine 0.3 mg kg^{-1}, 30 min before skin incision. We now doubt that a clinically useful application of pre-emptive analgesia with morphine is possible given the restraints of returning to spontaneous respiration at the end of surgery.

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A qualitative systematic review of incisional local anaesthesia for postoperative pain relief after abdominal operations

S. Møiniche, S. Mikkelsen, J. Wetterslev and J. B. Dahl

Summary

In a qualitative systematic review, we have evaluated randomized controlled trials (RCT) of incisional local anaesthesia compared with placebo or no treatment in the control of postoperative pain after open abdominal operations. Twenty-six studies with data from 1211 patients were considered appropriate for analysis. Five RCT considered inguinal herniotomy, four hysterectomy, eight cholecystectomy and nine studies a variety of surgical procedures. Outcome measures were pain scores, supplementary analgesics and time to first analgesic request. Efficacy was estimated by significant difference ($P<0.05$), as reported in the original investigation. All studies of herniotomy showed a 2–7-h duration of clinically relevant improved pain relief. Results of hysterectomy studies were inconclusive, with two being negative. Five of the cholecystectomy studies showed significant differences but questionable clinical importance and validity in three. In various other procedures results were inconsistent and in some of minor clinical importance. Except for herniotomy, there was a lack of evidence for effect of incisional local anaesthesia on postoperative pain and further standardized studies are needed before recommendations can be made. (*Br. J. Anaesth.* 1998; **81**: 377–383).

Keywords: anaesthesia, audit; anaesthetics local; surgery, laparotomy; surgery, herniotomy, pain, postoperative

The use of wound infiltration with local anaesthesia for postoperative pain relief may be an attractive method because of its simplicity, safety and low cost. However, despite widespread use, wound infiltration is still inconsistently and randomly used by many surgeons and anaesthetists. Even though a great number of original articles and some reviews have been published on this issue, there is little consensus available on when and after which surgical procedures incisional local anaesthesia may provide clinically relevant alleviation of postoperative pain. Of special interest may be to what extent differences in surgical procedure or involvement of visceral components influence efficacy.

In this systematic review, we have investigated the effect of wound infiltration with local anaesthesia for postoperative pain control, assessed using pain scores, need for and use of supplementary analgesics and/or time to first request for analgesics, using the evidence from all relevant randomized controlled and blinded studies. We have also examined trial methodology.

Methods

Reports of prospective, randomized, controlled trials (RCT) with or without open therapeutic control of wound infiltration with local anaesthesia were sought systematically. Reports were identified using the Cochrane Library, issue 4, and MEDLINE 1966–1997, without language restriction. Search terms included "wound infiltration", "incisional", "postoperative pain", "local anaesthesia", "bupivacaine", "lidocaine", "mepivacaine", "ropivacaine", "surgery". Reference lists of retrieved reports and review articles were also searched systematically for articles concerning local anaesthesia and postoperative pain. No abstracts or unpublished observations were included. Authors were not contacted for original data. Reports included were double-blinded, randomized comparisons of local anaesthesia with placebo (saline) or non-placebo (no treatment). Only articles dealing with abdominal incisions, that is laparotomies and herniotomies, and only those describing administration of *incisional* local anaesthesia were included. Incisional local anaesthesia was defined as infiltration, topical administration or instillation of local anaesthesia of, for example, skin, subcutaneous tissue, fascia, muscle and/or the parietal peritoneum. Furthermore, only reports considering adult patients (age >15 yr) were included.

Reports not included were those not stating pain outcome and reports of studies not randomized and double-blind. Studies of laparoscopic surgery and other surgical procedures, such as thyroidectomy, hemilaminectomy, haemorrhoidectomy, odontological surgery, tonsillectomy and arthroscopy were not considered. Also, studies where nerve blocks or *intra*peritoneal local anaesthetic instillation, or infiltration of viscera were performed were excluded. Finally, reports of comparisons of local anaesthetic wound infiltration with other treatments were not considered.

Each report which met the inclusion criteria was read independently by each of the authors and scored using a three-item, 1–5 score quality scale.[1] Consensus was then achieved. If the reports were described as randomized, 1 point was given, and an

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Table 1 Inguinal herniotomy. $P<0.05$=significant difference between local anaesthetic group and control group, ns=no significant difference, — =not evaluated

Study	Quality score	No. of Patients active/control	Pain score	Suppl. analgesic consumption	Time to first analgesic request	Comments
Sinclair and colleagues, 1988[10]	3	10/10/10	$P<0.05$	$P<0.05$	—	Significant over first 24-h period compared with placebo and no treatment, not later
Tverskoy and colleagues, 1990[14]	3	12/12	$P<0.05$	ns	$P<0.05$	Fixed analgesia after operation, pain score significant for 48 h
Bays and colleagues, 1991[11]	5	17/6/7	$P<0.05$	$P<0.05$	$P<0.05$	Pain score significant at 1, 3, 5 and 7 h, not later compared with placebo and no treatment
Dierking and colleagues, 1994[12]	4	14/14	$P<0.05$	$P<0.05$	$P<0.05$	Pain score significant at 1, 4 and 6 h, not later
Johansson and colleagues, 1997[13]	3	43/43/44	$P<0.05$	$P<0.05$	$P<0.05$	Pain score significant at 3 and 6 h for 0.5% and at 3 h for 0.25%

additional point given if the method of randomization was described and considered adequate (computer-generated, table of random numbers, etc) but 1 point was deducted if randomization was inappropriate (alternate randomization, randomization according to weekday, etc). If studies were described as double-blind, 1 point was given. An additional point was given if blinding was described and considered appropriate (blinded pharmacy manufactured ampoules, etc) but 1 point was deducted if blinding was inappropriate (comparisons of catheter treatment *vs* no treatment, etc) Finally, reports which described the numbers and reasons for withdrawals were given 1 point. By definition, studies without randomization and blinding were excluded. Thus the minimum score of an included RCT was 2 and the maximum score was 5. Information on type of anaesthesia (general or regional), number of patients enrolled and adverse effects was taken from each report.

Postoperative effectiveness was evaluated by significant difference ($P<0.05$, as reported in the original investigation) in pain relief, assessed using pain scores (visual analogue score or similar scores), time to first request for supplementary analgesia and consumption of supplementary analgesics compared with control. The sensitivity of evaluated non-significant studies (power of statistical tests) was considered. Any statistical power analysis of individual studies was noted.

Results

We identified 34 reports of incisional local anaesthesia. Of these, eight studies were excluded because of inappropriate blinding[2–8] or randomization.[9] In appendix A, a list of excluded studies is given. The remaining 26 reports were divided into those considering inguinal herniotomy (five), abdominal hysterectomy (four), open cholecystectomy (eight) and various types of abdominal surgery (nine). A total of 1211 patients, of whom 650 received local anaesthesia, were studied. The range of numbers of patients included in the studies was 20–130. The median quality score was 3 (range 2–5). Details of the included studies are shown in tables 1–4.

INCISIONAL LOCAL ANAESTHESIA FOR POSTOPERATIVE PAIN RELIEF AFTER INGUINAL HERNIOTOMY

In five studies, treatment arms compared incisional local anaesthesia with incisional saline[10–13] and/or no treatment (table 1).[10,11,14] Bupivacaine 0.25% 40 ml or 0.5% bupivacaine 15 ml was used in three studies,[11,12,14] lidocaine 200 mg in one study[10] and 0.25% and 0.5% ropivacaine 40 ml in the last study.[13]

All five studies showed significantly lower pain scores, with VAS reductions of approximately 25–50 mm (fig. 1). In three studies, pain scores were reduced at 1–7 h after surgery but not later.[11–13] In the study of Sinclair and colleagues,[10] pain scores were reduced over the first 24-h period but not during 24–48 h. In the study of Tverskoy and colleagues,[14] pain scores were reduced up to 48 h after operation. In the four studies where time to first analgesic request was evaluated,[11–14] significant prolongation in pain relief was observed at 2–7 h. In the study of Tverskoy and colleagues,[14] postoperative analgesia was thereafter fixed by study design, but supplementary analgesic consumption was significantly reduced by approximately 50% compared with control in the four other studies.[10–13]

INCISIONAL LOCAL ANAESTHESIA FOR POSTOPERATIVE PAIN AFTER ABDOMINAL HYSTERECTOMY

Two of four studies on abdominal hysterectomy compared incisional local anaesthesia with saline[15,16] and two with no treatment (table 2).[17,18] In the study of Sinclair and colleagues,[15] 500 mg of lidocaine

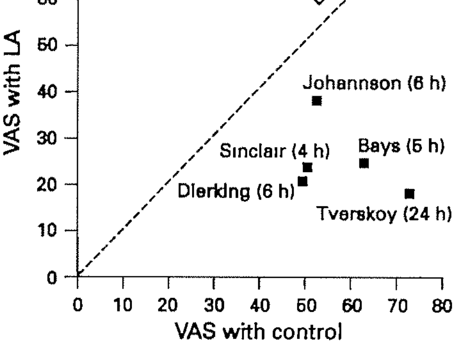

Figure 1 Mean or median visual analogue scale pain score (VAS, mm) for incisional local anaesthesia (LA) *vs* control in studies of inguinal herniotomy at the specific times shown. Each square represents an individual study. In all studies VAS was significantly ($P<0.05$) lower in the LA group compared with controls.

Table 2 Abdominal hysterectomy. $P<0.05$=significant difference between local anaesthetic group and control group, ns=no significant difference, — =not evaluated

Study	Quality score	No. of patients active/control	Pain score	Suppl. analgesic consumption	Time to first analgesic request	Comments
Sinclair and colleagues, 1996[15]	3	15/15	$P<0.05$	$P<0.05$	—	Significant over first 24 h period, not later
Hannibal and colleagues, 1996[16]	4	20/21	ns	$P<0.05$	—	Significant over 24 h observation periods, at day 1, 2, and 3
Cobby and Reid, 1997[17]	2	20/20	ns	ns	—	Observed for 6 h
Victory and colleagues, 1995[18]	3	18/19/19	ns	ns	—	Pre- *vs* postoperative *vs* no treatment observed 4, 8, 24, 48 and 96 h, analgesic consumption over 24 h periods

Table 3 Open cholecystectomy. $P<0.05$=significant difference between local anaesthetic group and control group, ns=no significant difference, — =not evaluated

Study	Quality score	No of patients active/control	Pain score	Suppl. analgesic consumption	Time to first analgesic request	Comments
Patel and colleagues, 1983[19]	4	17/23	—	$P<0.05$	—	Significant over 24 h periods, day 1–3
Thomas and colleagues, 1983[23]	4	10/10/10	—	($P<0.05$)	—	Significant over a 0–48 h observation period, when compared with no treatment but not compared with placebo
Levack and colleagues, 1997[24]	2	25/25	—	$P<0.05$	—	Significant over a 78 h observation period
Chester and colleagues, 1989[25]	3	15/15	$P<0.05$	$P<0.05$	—	Significant at day 1 and day 2
Van Raay and colleagues, 1992[20]	3	25/25	—	ns	—	Observed over 24 h periods from day 1–4
Adams and colleagues, 1991[21]	3	40/40	ns	ns	ns	Observed over 24 h and 72 h
Russell and colleagues, 1993[22]	4	14/16	ns	ns	—	Observed over 24 h
Johansson and colleagues, 1994[26]	3	22/22/22	$P<0.05$	$P=0.051$	$P<0.05$	Significant for 0.25%, not 0.125%, at 6 h but not later

aerosol administered subcutaneously caused a significant reduction of approximately 50% in pain scores and supplementary analgesic consumption during the first 24 h of the study, but not later. In the study of Hannibal and co-workers,[16] 0.25% bupivacaine 45 ml infiltrated subfascially and subcutaneously caused a 50% reduction in analgesic consumption but not in pain scores or time to first analgesic request. In contrast, subcutaneous infiltration of 0.5% bupivacaine 40 ml before or after operation compared with no treatment,[18] and subcutaneous infiltration of 0.5% bupivacaine 20 ml[17] demonstrated no improvement in analgesia. In these two negative studies, power analysis of the statistical tests revealed a risk of type II error of 20%.

INCISIONAL LOCAL ANAESTHESIA FOR POSTOPERATIVE PAIN AFTER OPEN CHOLECYSTECTOMY

Seven of eight studies compared 0.25–0.5% incisional bupivacaine 40–55 ml as a single dose[19–22] or infusion of 10–16 ml every 4–12 h,[23–25] with saline[19–26] or no treatment (table 3).[23] One study compared 0.125% and 0.25% incisional ropivacaine with saline.[26]

In three studies[19 23 24] there were no data on pain assessment but all three showed a decrease in supplementary analgesic consumption after incisional bupivacaine, although in one study the clinical significance was questionable[24] as methadone requirements over a 78-h period were reduced only from 84 mg in the control group to 61 mg in the treatment group.[24] Furthermore, in the study by Thomas, Lambert and Lloyd Williams,[23] incisional local anaesthesia was compared with both placebo and no treatment, and an effect was observed only in comparison with no treatment. In another study,[25] a bolus dose followed by continuous infusion of 0.5% bupivacaine 4 ml h^{-1} via a subfascially placed catheter caused significantly decreased pain scores and a 50% reduction in analgesic consumption on the first and second days after operation.[25] However, there was no effect on pain scores, total analgesic consumption or time to first analgesic request in three other studies.[20–22] Information on statistical power was not provided in any of these studies. In contrast, Johansson and co-workers[26] observed significantly reduced pain scores, time to first analgesic request and reduced supplementary analgesic consumption ($P=0.051$) at 6- h only. Furthermore, there was a significant dose–response relationship between saline 70 ml, and 0.125% and 0.25% ropivacaine.[26]

INCISIONAL LOCAL ANAESTHESIA FOR POSTOPERATIVE PAIN AFTER VARIOUS MAJOR AND MINOR SURGICAL PROCEDURES

Nine studies considered various major and minor procedures (table 4).[27–35] In the three studies on Caesarean section,[27–29] 0.25% or 0.5% bupivacaine 20 ml caused a 20–50% reduction in analgesic consumption.[27–29] However, this effect lasted for only 4 h.

Table 4 Various major and minor procedures. $P<0.05$=statistical significant difference between local anaesthetic group and control group, ns=no significant difference between local anaesthetic group and control group, — =not evaluated

Study	Surgical procedure	Quality score	No of patients active/control	Pain score	Suppl. analgesic consumption	Time to first analgesic request	Comments
Trotter and colleagues, 1991[27]	Caesarean section	4	14/14	ns	$P<0.05$	—	Significant at 4 h only, not later
Mecklem and colleagues, 1995[29]	Caesarean section	5	35/35	ns	$P<0.05$	—	Significant over 24 h Pain score ns except at 24 h
Ganta and colleagues, 1994[28]	Caesarean section	3	20/21	$P<0.05$	$P<0.05$	—	Significant at 4 and 12 h, not at 8 h
Partridge and colleagues, 1990[32]	Major upper/lower abdominal surgery	4	10/10	$P<0.05$	$P<0.05$	—	Pain score significant only in recovery room. Analgesic consumption significant over 24 h
Bartholdy and colleagues, 1994[33]	Major upper abdominal surgery	4	19/21	$P<0.05$	$P<0.05$	—	Pain score significant up to 12 h, not later. Analgesic consumption significant over 24 h periods from day 1–3
Pfeiffer and colleagues, 1991[34]	Abdominal aortic surgery	3	37/33	ns	ns	—	Observed over 24 h and 72 h
Turner and Chalkiadis, 1994[30]	Appendectomy	3	29/32/29	ns	ns	—	Pre- *vs* postoperative *vs* no treatment. Day 1 and day 2, evaluated at 12, 24 and 36 h
Willard and Blair, 1997[31]	Appendectomy	3	21/22	ns	ns	—	Evaluated in recovery room and every day until day 5
Holst and colleagues, 1992[35]	Minor gynaecological laparotomy	3	12/12	$P<0.05$	ns	—	Significant at 2 h only, not later

Furthermore, in only one study[28] were pain scores reduced compared with control. Two studies[32 33] considered a combination of several major surgical procedures (stomach, hepatic, biliary, pancreatic and ventral hernia, etc) and one investigated abdominal aortic surgery.[34] In these studies, 0.25% bupivacaine 30–40 ml was infiltrated subcutaneously and subfascially.[32–34] No firm evidence of a beneficial effect of local anaesthesia was obtained. In one study,[33] only a slight reduction in daily morphine ingestion (10 mg) was noted, and a reduction in VAS only during mobilization was recorded (50 mm).[33] In another study,[32] a 30% reduction in VAS and a reduction in opioid ingestion (pethidine 150 mg) was reported.[32] There was no analgesic effect after aortic surgery[34] (0.25% bupivacaine 40 ml). Furthermore, in two studies of appendectomy[30 31] where 1.5% lidocaine 15 ml was infiltrated into the skin, subcutaneous tissue and subfascia[30] before or after operation compared with saline, or a mixture of 1% lidocaine and 0.25% bupivacaine 44 ml was infiltrated into all layers of the surgical incision,[31] no effect was observed in pain scores or supplementary analgesic consumption in the recovery room[31] and over 12-h periods.[30] Finally, a reduction in pain scores was observed at 2 h only after operation but there were no differences in total analgesic consumption after minor gynaecological operations.[35] Power analysis was not performed in any of the negative studies.

ANAESTHESIA AND ADVERSE EFFECTS

Surgical procedures were performed under general anaesthesia in all except for one study (Caesarean section, spinal anaesthesia).[29] In one study major upper abdominal procedures[33] were performed under combined thoracic extradural and general anaesthesia. However, regional anaesthesia in these studies did not seem to mask the effect of incisional local anaesthesia as both showed improved pain relief.

No adverse effects attributable to incisional local anaesthesia were reported.

Discussion

In this systematic review, we have evaluated the effect of incisional local anaesthesia for control of postoperative pain. More than 90 studies of incisional and peripheral administration of local anaesthesia have been published in a variety of surgical procedures and surgical populations. Because of the large variability in study design, where incisional local anaesthetic infiltration has been combined with, for example, visceral local anaesthetic infiltration, nerve block or other treatments, results are inconclusive. In order to eliminate as many confounding factors as possible, we chose to review only those studies where abdominal incisions were performed, using the strict inclusion and exclusion criteria described, in order to evaluate the effect of incisional local anaesthesia *per se*. Abdominal incisions performed for laparoscopic surgery (trocar and port-sites) where not considered because of the possible confounding effect of peritoneal irritation after carbon dioxide insufflation. We selected 26 RCT with data analysed from more than 1200 patients. Even though aiming to standardize surgical procedure, interpretation was difficult, especially because of the small number of studies (e.g. only four studies of hysterectomy, two studies of appendectomy, etc).

However, data consistently showed a statistical in addition to a clinically significant effect after inguinal herniotomy. However, in most studies the effect was short-lived (2–7 h). These data reflect the fact that

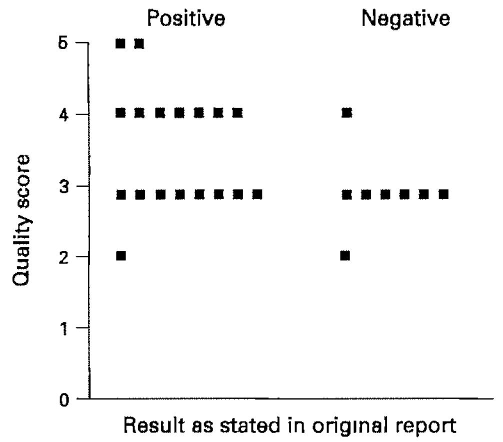

Figure 2 Efficacy of incisional local anaesthetics. Relationship between quality of studies and estimation of efficacy, as reported in the original investigation. Each square represents an individual study. "Positive" refers to studies with statistical significance between the local anaesthetic group and controls group, "negative" refers to studies not statistically significant.

inguinal herniotomy may be performed under local anaesthetic infiltration only.[36–38] It is difficult to explain the long-lasting pain reducing effect observed in the study of Tverskoy and colleagues.[14] Although claimed to be a result of a pre-emptive effect, many have disputed this hypothesis.[18,30,39–44]

Interpretation of the differences in results after hysterectomy[15–18] is difficult. However, wider application of local anaesthesia (subcutaneously and subfascial), as in the study of Hannibal and colleagues,[16] may be important. Furthermore, a possible masking effect of a rather large dose of intraoperative opioid in the study of Victory and colleagues[18] may also have played a role.

The large variability in study design after open cholecystectomy hindered interpretation. Some studies only considered intraoperative administration of local anaesthesia while others investigated postoperative infusion or repeated injections of local anaesthesia.

Five of eight studies on open cholecystectomy were positive for at least one of the evaluated pain outcome measures. However, in three of these positive studies,[19,23,24] there were no data on pain assessment making validation difficult, and in one study[23] only the comparison with no treatment but not with placebo was positive. There is no clear explanation for this disparity. In most studies the local anaesthetic was distributed widely to the cut surfaces of the peritoneum, fascia and subcutaneous tissue. Furthermore, there were no major differences in dose of local anaesthetic (volume and concentration). However, the well-designed positive study of Johansson and colleagues[26] was convincing as a significant dose–response relationship was observed. But the analgesic effect was short-lived.

Although short-lasting and without reduced pain scores in two of three studies,[27,29] the reduction in the need for supplementary analgesia observed after Caesarean section[27–29] may be clinically relevant in this special category of patients. Thus data from these studies may indicate an early beneficial effect of incisional local anaesthesia. However, because of the few studies available after this procedure, the validity of this conclusion may be questioned.

The same applies to the two studies after appendectomy.[30,31] However, the lack of analgesic effect may be a result of a significant inflammatory visceral component which may have masked any beneficial effect of the somatic neural block. Nevertheless, no evidence for improved pain relief after appendectomy has been observed in adult patients, although improved pain relief has been shown after *paediatric* appendectomy.[45]

The clinical beneficial effect observed after various other major procedures[32,33] may be questionable as only small reductions in supplementary analgesics were observed. Of importance may be that different surgical procedures were studied within these investigations[32,33] and that severe visceral pain after the major trauma of some of these procedures (e.g. aortic surgery, Whipple) may have masked any minor beneficial somatic effect of incisional local anaesthesia.

Of a total of 26 studies, eight were unequivocally negative. Even though the majority of studies showed significant differences in at least one pain measure, several were of questionable clinical importance. It is surprising that local anaesthesia was not associated with more consistent positive results. There may be several explanations for this.

First, when analysing study quality, in 50% of the positive studies, quality scores were 4 or 5 whereas in only one of the eight negative studies the score was more than 3 (fig. 2). This is in contrast with a recent review of the analgesic efficacy of peripheral opioids[46] where studies of lower quality were more likely to over-estimate the efficacy of treatments. Nevertheless, the general quality of studies examined in this review was relatively high, with only one negative and one positive study having the minimum score of 2.

Second, another point worth emphasizing is the sample size of the individual studies. Risk of bias exists when comparing studies of a large number with those of a small number. The risk of a type II error depends partly on study size. In only two of the negative studies was a power analysis performed. However, the mean number of patients per study was approximately 55 for the negative studies and approximately 40 patients for the positive studies. With these numbers, we consider the risk of major bias on this account small. Eventually, as stated in a recent study by Tramèr and colleagues,[47] quantitative analysis was impossible because the studies examined constituted a variety of different study designs, drugs, doses and application sites.

Third, of greater importance may be the technique used for administration of local anaesthesia. Only few studies addressed the importance of the relative contribution of different anatomical structures to postoperative pain. For example, a recent study showed that lidocaine was more effective when applied subfascially compared with subcutaneously after hernia repair.[48] Furthermore, it would not be unreasonable to expect improved pain relief if visceral structures are also infiltrated with local anaesthesia, as shown in studies of laparoscopic surgery where viscerally applied local anaesthetics, in addition to port-site wound infiltration alone, caused improved pain relief.[49,50] Finally, in the studies of Johansson and colleagues after herniotomy[13] and cholecystectomy,[26] a significant dose–response relationship of incisional local anaesthesia was observed where the largest dose (highest concentration) of the local anaesthetic caused the most pronounced pain relief. Not surprisingly, it may be of importance *where* and *how much* local anaesthetic is used.

With the exception of herniotomy, this review revealed an overall lack of evidence for any important effect (rather than evidence for a lack of effect) of incisional local anaesthesia in most abdominal procedures despite the numerous studies available. Therefore, the use of incisional local anaesthesia should be reserved for herniotomy until further well-designed studies with a strictly standardized methodology are available. The literature provides no support for an analgesic effect outlasting the pharmacological effect of incisional local anaesthesia.[44 51]

Appendix

Table 1A Excluded studies

Excluded study	Reason for exclusion
Hashemi and Middleton, 1983[4]	Not blinded as only the treatment group had a subcutaneous catheter inserted
Gibbs and colleagues, 1988[3]	No information on blinding
Egan and colleagues, 1988[5]	No information on blinding of observer
Erikson-Mjoberg and colleagues, 1997[2]	Single-blinded, only blind to the patients
Cameron and Cross, 1985[6]	Not blinded as only the treatment group had a subcutaneous catheter inserted
Huang and colleagues, 1997[7]	No information on blinding of patients
Bielechi and Szepietowski, 1989[8]	No information on blinding
Ben-David and colleagues, 1995[9]	Inappropriate randomization as a result of alternating allocation to study groups

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High-dose ondansetron regimen *vs* droperidol for morphine patient-controlled analgesia

M. DRESNER, S. DEAN, A. LUMB AND M. BELLAMY

Summary

We have performed a randomized, double-blind study comparing droperidol and high-dose ondansetron mixed with morphine for patient-controlled analgesia (PCA). To detect a reduction in the incidence of postoperative nausea and vomiting from 55% to 20% with a power of 80% at the $P<0.05$ level, 29 patients per group were required. We studied 60 healthy women undergoing abdominal hysterectomy, anaesthetized using a standard technique. Group D received a bolus dose of droperidol 1.25 mg at induction followed by droperidol 0.1 mg per 1 mg of morphine from the PCA system. Group O received a bolus dose of ondansetron 4 mg at induction followed by ondansetron 0.32 mg per 1 mg of morphine. This dose of ondansetron is more than double that studied previously. Mean nausea and vomiting scores at 4, 8, 12 and 24 h, mean time to first vomit, sedation scores, incidence of side effects, and doses of prochlorperazine did not differ between the groups. In group D, 24 patients did not vomit compared with 23 in group O. The only significant difference between the groups was increased morphine consumption in the ondansetron group up until 12 h after operation ($P<0.05$), but by 24 h this difference was not significant. The ondansetron regimen was more expensive (at local prices) by a factor of 27, and our results suggested no clinical advantage over droperidol. (*Br. J. Anaesth.* 1998; **81**: 384–386).

Keywords: vomiting, incidence; vomiting, antiemetics; pharmacology, ondansetron; pharmacology, droperidol; analgesia, patient-controlled

Patient-controlled analgesia (PCA) is an effective, safe and labour-saving technique for providing postoperative pain relief.[1] However, its use does not solve the problem of postoperative nausea and vomiting (PONV).[2,3] Droperidol,[4–7] ondansetron[8] and combinations of the two[9] have been shown to reduce the incidence of PONV when added to morphine in a patient-controlled analgesia system (PCAS). In this study, we have compared the efficacy, side effects and cost of a high-dose ondansetron regimen with droperidol.

Patients and methods

A previous study showed that the incidence of postoperative vomiting associated with morphine and droperidol PCAS was 51%.[8] To detect a reduction in the incidence of PONV from 55% to 20% with a power of 80% at the $P<0.05$ level, 29 patients per group were required. After obtaining approval from the Clinical Research (Ethics) Committee, written informed consent was obtained from all patients. Patients with allergies to any of the drugs or history of severe PONV were excluded. We studied 60 ASA I–II women undergoing abdominal hysterectomy via a Pfannenstiel incision for benign disease.

All patients were anaesthetized by one of the authors using a standard anaesthetic technique. Premedication comprised oral diazepam 10 mg, 1 h before surgery. The induction sequence consisted of fentanyl 4 μg kg^{-1}, an induction dose of propofol 2–3 mg kg^{-1} with lidocaine 1 mg ml^{-1}, atracurium 0.5 mg kg^{-1} and intubation with a 7.5-mm tracheal tube. Patients' lungs were ventilated to normocapnia with 0.6–1.2% isoflurane (end-expiratory) and 70% nitrous oxide in oxygen, and antagonized with glycopyrrolate 7 μg kg^{-1} and neostigmine 40 μg kg^{-1}.

Patients were allocated randomly to one of two groups after induction of anaesthesia. Each patient received a loading dose of the appropriate antiemetic and the PCAS mixture was prepared. The drug combination for group D was a loading dose of droperidol 1.25 mg, and a mixture of morphine 1 mg ml^{-1} with droperidol 0.1 mg ml^{-1} in the PCAS. Group O received a loading dose of ondansetron 4 mg and a PCAS mixture of morphine 1 mg ml^{-1} with ondansetron 0.32 mg ml^{-1}. Graseby PCAS pumps (Graseby Medical Ltd, Watford, Herts, UK) were used, set to deliver a loading dose of morphine 5 mg on the first request, followed by 1-mg bolus doses of morphine with a 5-min lockout period. All patients received oxygen, and vital signs, ventilatory frequency and conscious level were monitored throughout PCAS therapy. Prochlorperazine 12.5 mg i.m. was prescribed at the discretion of nursing staff.

PONV, prochlorperazine usage, pain, sedation, antiemetic side effects and morphine consumption were recorded by ward nurses blinded to the treatment group at 4, 8, 12 and 24 h after operation, using the verbal rating scores shown in table 1. PCAS syringes were refilled when appropriate by an on-call

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Table 1 Observation record, repeated at 4, 8, 12 and 24 h after surgery

Nausea since surgery	0	None
	1	Mild, intermittent nausea
	2	Constant, moderate nausea
	3	Severe nausea
Vomiting since surgery	0	None
	1	One vomit only
	2	Several vomits
	3	Repeated retching/vomiting
Prochlorperazine given?	Yes/No	
Pain score	0	No pain
	1	Slight pain
	2	Moderate pain
	3	Severe pain
Sedation level	0	Alert
	1	Drowsy
	2	Sleeping, but rousable
	3	Unrousable
Side effects		Extrapyramidal signs Restlessness/anxiety Headache
PCAS morphine used	mg	

Table 2 Patient characteristics (median (range))

	Group D (droperidol, n=30)	Group O (ondansetron, n=30)
Age (yr)	46 (29–60)	45 (28–57)
Weight (kg)	64 (48–84)	63 (46–88)

anaesthetist who was aware of the patient's treatment group.

Results were analysed using SPSS. Chi-square with Yates' correction and the Mann–Whitney *U* test were used as appropriate; time to first episode of vomiting was analysed by Kaplan–Meier plotting and the log rank test. $P<0.05$ was regarded as significant.

Results

There was no difference between the groups in age or weight (table 2).

The results are shown in table 3. Apart from morphine use in the first 12 h, there were no significant differences between the groups.

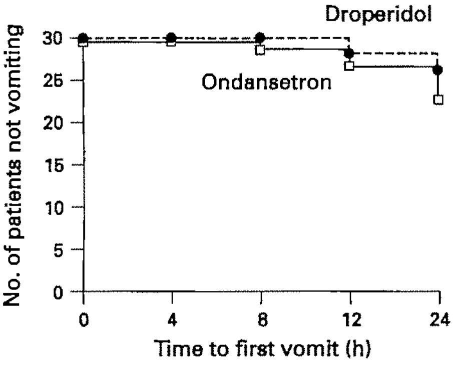

Figure 1 Time to first episode of vomiting in the ondansetron and droperidol groups.

Table 3 Nausea and vomiting, pain and sedation scores and morphine consumption in the two groups. Values in parentheses refer to the number of patients affected by any nausea or vomiting scores at that time

	Group D	Group O
Mean nausea score at:		
4 h	0.47 (12)	0.5 (12)
8 h	0.4 (11)	0 63 (14)
12 h	0.37 (9)	0.43 (12)
24 h	0.37 (4)	0 57 (7)
Mean vomiting score at:		
4 h	0 (0)	0 (0)
8 h	0 (0)	0.03 (1)
12 h	0.1 (2)	0.1 (3)
24 h	0.23 (4)	0.33 (7)
No. who never vomited	24	23
Doses of prochlorperazine given?	14	14
Mean pain score at:		
4 h	1.53	1 8
8 h	1.33	1.2
12 h	0.97	1.07
24 h	0.23	1.3
Mean sedation score at:		
4 h	1.13	1.13
8 h	0.93	0.7
12 h	0.97	0.77
24 h	0.3	0.23
Headaches	3	6
Anxiety/restlessness	0	0
Extrapyramidal symptoms	0	0
PCAS morphine used by:		
4 h	18.87	28 93 ($P<0.0086$)
8 h	26.47	38 63 ($P<0.0033$)
12 h	32.9	44.77 ($P<0.0376$)
24 h	43.6	56.67

Table 4 Cost per patient of the antiemetic regimens

	Group D	Group O
Cost per 50 mg of morphine	£0.93	£24 74
Cost per patient	£1.27	£34.72

Time to first vomit is shown in figure 1. There were no significant differences between the groups.

Mean cost per patient of the two antiemetic regimens, at local prices, is shown in table 4, and takes into account the greater need for second syringes in group O. Droperidol costs assume taking the bolus and infusion doses from a single ampoule. Prices include value added tax.

Discussion

Droperidol, a butyrophenone, acts primarily as a dopamine (D_2) antagonist. In the prevention of PONV, several studies have demonstrated its superiority over placebo, either as a bolus dose before PCA therapy[4] or mixed with morphine in ratios of 0.05 mg:1 mg[5 6] to 0.17 mg: 1 mg.[10] Despite the improvements, nausea was still seen in 30–50% of patients treated with droperidol.

Ondansetron is a highly selective 5-hydroxytryptamine type 3 receptor antagonist which acts peripherally on vagus nerve endings and centrally on the chemoreceptor trigger zone. Given in two 4-mg boluses, it has been shown to be similar to placebo during PCA.[9] After loading with 4 mg, a concentration of ondansetron 0.13 mg per 1 mg of morphine has been shown to be as good, but not better than droperidol.[8 11] Our study showed that increasing the infused concentration of ondansetron to 0.32 mg per 1 mg of morphine failed to improve on the efficacy of droperidol. The only study in which ondansetron performed better than droperidol using a PCA involved droperidol 0.1 mg *and* ondansetron 0.13 mg per 1 mg of morphine.[11] Even then, the combination proved superior to droperidol or ondansetron alone only for the first 12 h.

The only difference between the two groups was lower morphine consumption in the first 12 h in the droperidol group. This could be related to the sedative effect of droperidol. However, there was no resultant difference in pain scores.

Our results and those of other studies support the use of droperidol as the first-line drug in preventing PONV associated with PCA. Ondansetron may have a role in patients for whom droperidol is unsuitable, but this study did not support the use of high-dose ondansetron in terms of efficacy or economics. The literature suggests a role for a combination regimen in patients with a history of severe PONV. Given the multifactorial causes, multiple receptors and diverse neural pathways involved in PONV, research into other multiple drug combinations would appear to be the logical way forward.

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Granisetron–droperidol combination for the prevention of postoperative nausea and vomiting in female patients undergoing breast surgery

Y. FUJII, H. TOYOOKA AND H. TANAKA

Summary

We have compared the efficacy and safety of the combination granisetron–droperidol with each antiemetic alone in preventing postoperative nausea and vomiting (PONV) after breast surgery. In a randomized, double-blind study, 150 female patients received granisetron 3 mg, droperidol 1.25 mg or granisetron 3 mg with droperidol 1.25 mg (n=50 each) i.v., immediately before induction of anaesthesia. A standard general anaesthetic technique was used. The incidence of PONV during the first 24 h after anaesthesia was 18% with granisetron, 38% with droperidol and 4% with the granisetron–droperidol combination ($P<0.05$; overall Fisher's exact probability test). We conclude that the granisetron–droperidol combination was more effective than each antiemetic alone in the prevention of PONV in female patients undergoing breast surgery. (*Br. J. Anaesth.* 1998; **81**: 387–389).

Keywords: surgery, breast; pharmacology, droperidol; pharmacology, granisetron; vomiting, nausea; vomiting, incidence; vomiting, antiemetics

Postoperative nausea and vomiting (PONV) are distressing adverse effects of anaesthesia and surgery, with a relatively high incidence in women undergoing breast surgery.[1 2] We have demonstrated that granisetron, a selective 5-hydroxytryptamine type 3 (5-HT$_3$) receptor antagonist, reduces the incidence of PONV after breast surgery.[3] None of the available antiemetics is entirely effective in the prevention of PONV, probably because most act through block of one receptor.[4] McKenzie and colleagues[5] have demonstrated recently that the combination of droperidol and ondansetron was more effective than droperidol alone in preventing PONV after gynaecological surgery.

In this study, we have compared the efficacy of a combination of granisetron and droperidol with each antiemetic alone, in the prevention of PONV in female patients undergoing breast surgery.

Patients and methods

After obtaining approval from our Institutional Review Board and informed patient consent, we studied 150 female patients, ASA I–II, aged 42–62 yr, undergoing elective breast surgery. Patients who had a history of motion sickness or previous PONV, or both, those who had gastrointestinal diseases, those who had received antiemetic medication within 24 h before surgery, and those who were menstruating or under hormonal therapy were excluded.

Patients were allocated randomly to one of three groups (n=50 each) to receive pretreatment with granisetron 3 mg, droperidol 1.25 mg or granisetron 3 mg with droperidol 1.25 mg. These were administered i.v. over 2–5 min immediately before induction of anaesthesia according to a randomization list generated by a random number function in a computer spreadsheet.

Patients received no premedication. Anaesthesia was induced with thiopental 5 mg kg^{-1} i.v., and vecuronium 0.2 mg kg^{-1} i.v. was used to facilitate tracheal intubation. After tracheal intubation, anaesthesia was maintained with 1.0–3.0% (inspired concentration) isoflurane and 66% nitrous oxide in oxygen. Isoflurane concentration was adjusted to maintain arterial pressure and heart rate within 15% of pre-induction values. Ventilation was controlled mechanically and adjusted to maintain an expired PE'_{CO_2} of 4.6–5.3 kPa (Ultima, Datex, Helsinki, Finland). A nasogastric tube was inserted and suction applied to empty the stomach of air and other contents. Before tracheal extubation, the nasogastric tube was suctioned and then removed. Further neuromuscular blocking agents were used as required. At the end of surgery, nitrous oxide and isoflurane administration was stopped, and atropine 0.02 mg kg^{-1} i.v. and neostigmine 0.05 mg kg^{-1} i.v. were administered for antagonism of neuromuscular block. The trachea was extubated when the patient was awake. Rectal temperature was monitored and maintained at 37±1°C using a hot water warming pad. If two or more episodes of PONV occurred during the first 24 h after anaesthesia, rescue antiemetic (domperidone) was given rectally. Analgesia consisted of indomethacin 50 mg rectally for moderate pain and buprenorphine 0.2 mg i.m. for severe pain.

After operation, all episodes of PONV experienced by the patient were recorded every 3 h during the first 24 h after anaesthesia (0–3 h in the post-anaesthesia unit and 3–24 h on the ward) by direct questioning by nursing staff blinded to the study group, or by spontaneous complaint by the patient. Nausea was defined as a subjectively unpleasant

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Table 1 Patient characteristics and type of operation (mean (SD or range) or number)

	Granisetron group (n=50)	Droperidol group (n=50)	Granisetron–droperidol combination (n=50)
Age (yr)	54 (43–65)	52 (43–64)	55 (43–68)
Height (cm)	154 (4)	154 (5)	154 (5)
Weight (kg)	55 (8)	54 (6)	54 (7)
Duration of operation (min)	109 (32)	113 (35)	112 (32)
Duration of anaesthesia (min)	133 (32)	137 (35)	112 (32)
Preoperative blood loss (ml)	223 (119)	214 (98)	214 (135)
Postoperative analgesic used (n)			
Indomethacin	27	28	27
Buprenorphine	8	7	7
Type of operation performed (n)			
Partial mastectomy	10	11	11
Partial mastectomy with axialry dissection	5	4	5
Modified radical mastectomy	7	8	7
Modified radical mastectomy with axialry dissection	28	27	27

Table 2 Incidence of PONV during the first 24 h after anaesthesia (number (%)). P_1 values: granisetron *vs* granisetron–droperidol combination; P_2 values: droperidol *vs* granisetron–droperidol combination

	Granisetron group (n=50)	Droperidol group (n=50)	Granisetron–droperidol combination (n=50)	P_1 values	P_2 values
PONV					
0–3 h	4 (8%)	7 (14%)	1 (2%)		
3–24 h	5 (10%)	12 (24%)	1 (2%)		
overall	9 (18%)	19 (38%)	2 (4%)	0.026	0.001
Nausea					
0–3 h	2 (4%)	3 (6%)	0 (0%)		
3–24 h	2 (4%)	6 (12%)	1 (2%)		
overall	4 (8%)	9 (18%)	1 (2%)	0.181	0.008
Retching					
0–3 h	0 (0%)	1 (2%)	0 (0%)		
3–24 h	0 (0%)	1 (2%)	0 (0%)		
overall	0 (0%)	2 (4%)	0 (0%)	1.0	0.247
Vomiting					
0–3 h	2 (4%)	3 (6%)	1 (2%)		
3–24 h	3 (6%)	5 (10%)	0 (0%)		
overall	5 (10%)	8 (16%)	1 (2%)	0.102	0.015

sensation associated with awareness of the urge to vomit; retching was defined as the laboured, spasmodic, rhythmic contraction of the respiratory muscles, including the diaphragm, chest wall and abdominal wall muscles without expulsion of gastric contents; vomiting was defined as the forceful expulsion of gastric contents from the mouth.[6] If patients had more than one symptom they were categorized as having experienced the most severe symptom (vomiting>retching>nausea). Adverse effects throughout the study were recorded by follow-up nurses who interviewed the patients and recorded spontaneous complaints.

Statistical analyses were performed by one-way analysis of variance (ANOVA) with Bonferroni correction for multiple comparison, chi-square test and Fisher's exact probability test, as appropriate (StatView 4.0; Macintosh). $P<0.05$ was considered significant. All values are expressed as mean (SD) or number (%).

Results

Patient data, including age, height, weight, and duration of surgery or anaesthesia, analgesics used after operation, and type of operation performed were not different between groups (table 1).

During the first 24 h after anaesthesia, the incidence of PONV was 18% with granisetron, 38% with droperidol and 4% with the granisetron–droperidol combination (table 2). The incidence of PONV in patients who had received granisetron with droperidol was significantly lower than that in those who had received granisetron alone or droperidol alone ($P<0.05$).

The most frequently reported adverse events were headache, dizziness and drowsiness (table 3), which were not serious. There were no differences in the incidence of adverse effects between groups.

Discussion

The incidence of PONV is relatively high in women undergoing general anaesthesia for breast surgery.[1 2] In our recent studies, the incidence of PONV after breast surgery was approximately 50% in this population.[3 7] This incidence justifies the use of prophylactic antiemetics for preventing PONV after breast surgery. The aetiology of PONV after breast surgery

Table 3 Adverse events (number). No significant differences

	Granisetron group (n=50)	Droperidol group (n=50)	Granisetron–droperidol combination (n=50)
Any adverse effects	9	10	10
Headache	4	4	4
Dizziness	2	2	2
Drowsiness	2	3	3
Other	1	1	1

performed under general anaesthesia is not known, but is probably multifactorial.[6] Several factors, including age, sex, obesity, history of motion sickness or previous PONV, operative procedure, anaesthetic technique and postoperative pain are thought to affect the incidence of PONV. In this study, these factors were well balanced between groups, and patients with a history of motion sickness or previous PONV, or both, were excluded. Therefore, differences in the incidence of PONV between groups can be attributed to differences in the antiemetic drugs administered.

Granisetron has already been shown to be an effective treatment for vomiting in patients receiving cytotoxic drugs.[8] We have demonstrated recently that it reduces the incidence of PONV in female patients undergoing breast surgery.[3,7] Although the precise mechanism for preventing PONV is not known, it has been suggested that granisetron may act on sites containing 5-HT$_3$ receptors with demonstrated antiemetic effects.[9] Droperidol is a major tranquilizing drug that has antiemetic activity as a result of its antagonistic property at the dopamine receptor.[6] There are no published studies comparing the combination of granisetron and droperidol with each antiemetic alone in the prevention of PONV after breast surgery. We demonstrated in this study that the incidence of PONV in patients who had received granisetron with droperidol (4%) was lower than that in those who had received granisetron alone (18%) or droperidol alone (38%) (P<0.05).

The effective dose of granisetron is 40–80 μg kg^{-1} for the treatment of cancer therapy-induced emesis.[10] As demonstrated previously, the efficacy of granisetron 40 μg kg^{-1} was the same as that of granisetron 80 μg kg^{-1} for reducing the incidence of PONV in patients undergoing breast surgery.[7] The dose of granisetron (3 mg, approximately 55 μg kg^{-1}) chosen for this study was within this range. The dose of droperidol 1.25 mg was chosen from previous work.[11,12]

One of the problems of using droperidol for prophylactic antiemetic therapy is the risk of undesirable adverse effects, such as excessive sedation and extrapyramidal signs.[6] The adverse effects observed in this study were not serious, and there were no differences in the incidence of headache, dizziness and drowsiness between the groups. Excessive sedation and extrapyramidal symptoms were not observed.

In summary, the combination of granisetron–droperidol was more effective than each antiemetic alone for the prevention of PONV in female patients undergoing breast surgery.

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Oral granisetron prevents postoperative vomiting in children

Y. Fujii, H. Toyooka and H. Tanaka

Summary

We have studied the efficacy of granisetron, a selective 5-hydroxytryptamine type 3 receptor antagonist, administered orally for the prevention of postoperative vomiting after tonsillectomy in children. In a randomized, double-blind, placebo-controlled study, 160 paediatric patients, ASA I, aged 4–10 yr, received placebo or granisetron (20, 40 or 80 μg kg^{-1}) (n=40 each) orally, 1 h before surgery. A standard general anaesthetic technique was used throughout. A complete response, defined as no emesis and no need for another rescue antiemetic during the first 24 h after anaesthesia, occurred in 40%, 48%, 85% and 90% of patients who had received placebo, or granisetron 20, 40 or 80 μg kg^{-1}, respectively (P<0.05; overall Fisher's exact probability test). There were no clinically important adverse events. We conclude that preoperative oral granisetron, in doses more than 40 μg kg^{-1}, was effective for the prevention of postoperative vomiting in children. (*Br. J. Anaesth.* 1998; **81**: 390–392).

Keywords: vomiting, incidence; vomiting, antiemetics; pharmacology, granisetron; children

The incidence of vomiting after tonsillectomy in children is high when no prophylactic antiemetic is provided.[1] A variety of pharmacological approaches (antihistamines, butyrophenones, dopamine receptor antagonists) have been investigated in the prevention and treatment of postoperative emesis, but undesirable adverse effects, such as excessive sedation, hypotension, dry mouth, dysphoria, hallucinations and extrapyramidal symptoms have been noted.[2] Ondansetron, a selective 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist, is a prophylactic antiemetic for the prevention of vomiting after tonsillectomy in children.[3 4] Granisetron, another new 5-HT_3 receptor antagonist, has more potent and longer acting properties than ondansetron,[5] and reduced the incidence of postoperative emesis in paediatric patients undergoing tonsillectomy with or without adenoidectomy.[6] However, granisetron is more expensive than other antiemetics, such as droperidol and metoclopramide, commonly used for the prevention of postoperative emesis. Oral granisetron is less expensive than the i.v. formulation and is effective against cisplatin-induced emesis.[7] We conducted a randomized, double-blinded, placebo-controlled study to determine the efficacy of oral granisetron in the prevention of postoperative vomiting in children undergoing tonsillectomy.

Patients and methods

After obtaining approval from the Institutional Review Board and informed parental consent, we studied 160 ASA I children, aged 4–10 yr, undergoing elective tonsillectomy with or without adenoidectomy. Children who had experienced postoperative vomiting, who had received antiemetic medication within 24 h before surgery, and who had a history of motion sickness were excluded.

Patients were allocated randomly to one of four groups (n=40 in each) using computer-generated random numbers concealed in envelopes, to receive orally either placebo or granisetron at three different doses (20, 40 or 80 μg kg^{-1}), 1 h before surgery. Syrups with and without granisetron were prepared for each study group by a pharmacist.

Solid food was not allowed after midnight and clear liquids were permitted up to 3 h before surgery. As premedication, all patients were given bromazepam 3 mg rectally, 1 h before operation. Anaesthesia was induced with sevoflurane and nitrous oxide in oxygen via a mask. Tracheal intubation was facilitated with vecuronium 0.1 mg kg^{-1} i.v. After tracheal intubation, anaesthesia was maintained with 0.5–3.0% sevoflurane (inspired concentration) and 66% nitrous oxide in oxygen. Ventilation was controlled mechanically and adjusted to maintain an end-tidal carbon dioxide partial pressure of 4.2–5.3 kPa using an anaesthetic–respiratory gas analyser (Ultima, Datex, Helsinki, Finland). Neuromuscular block was achieved with vecuronium and antagonized by a combination of atropine 0.02 mg kg^{-1} and neostigmine 0.04 mg kg^{-1} i.v. at the end of surgery. Before tracheal extubation, the nasal or orogastric tube was inserted and suction applied to empty the stomach of air or other contents, and then the tube was removed. The trachea was extubated when the patient was awake. Rectal temperature was monitored and maintained at 37±1°C throughout surgery. After operation, all patients were admitted to the hospital and remained for 2 days. Clear liquids were offered only if the

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Table 1 Patient data (mean (SD or range) or number). No significant differences

	Placebo (*n*=40)	Granisetron 20 μg kg^{-1} (*n*=40)	Granisetron 40 μg kg^{-1} (*n*=40)	Granisetron 80 μg kg^{-1} (*n*=40)
Age (yr)	6.9 (4–10)	6.5 (4–10)	6.3 (4–10)	6.6 (4–10)
Sex (M/F)	18/22	18/22	17/23	18/22
Height (cm)	121.2 (11.5)	120.8 (11.8)	118.2 (10.4)	119.6 (12 4)
Weight (kg)	24.7 (6.6)	25.2 (7.5)	23.5 (5 6)	24.5 (7.1)
Duration of operation (min)	62 (21)	59 (16)	58 (17)	61 (17)
Duration of anaesthesia (min)	85 (20)	80 (15)	78 (16)	83 (17)
Analgesics used after operation				
Paracetamol (mg)	250 (68)	250 (75)	238 (59)	253 (68)
Pentazocine (mg)	1.6 (3.2)	1.5 (3 1)	1.5 (3.1)	1 6 (3.3)
Type of surgery (*n*)				
Tonsillectomy	18	19	18	19
Tonsillectomy with adenoidectomy	22	21	22	21

Table 2 Number of patients (%) with a complete response (no retching, no vomiting and no rescue), retching and vomiting, and those who required rescue antiemetic during the first 24 h after anaesthesia. *P* values *vs* placebo

	Placebo (*n*=40)	Granisetron 20 μg kg^{-1} (*n*=40)	*P*	Granisetron 40 μg kg^{-1} (*n*=40)	*P*	Granisetron 80 μg kg^{-1} (*n*=40)	*P*
Complete response	16 (40%)	19 (48%)	0.326	34 (85%)	0.001	36 (90%)	0.001
Retching	13 (33%)	11 (28%)	0.404	4 (10%)	0 013	2 (5%)	0.005
Vomiting	14 (35%)	12 (30%)	0.406	3 (8%)	0 003	3 (8%)	0 003
Rescue	9 (23%)	8 (20%)	0.5	0 (0%)	0.001	0 (0%)	0 001

patient requested, and other oral fluids were was not allowed for 4 h after recovery from anaesthesia. If two or more episodes of vomiting occurred during the first 24 h after anaesthesia, another rescue antiemetic (e.g. domperidone rectally) was given. Postoperative analgesia was provided with paracetamol 10–25 mg kg^{-1} rectally for mild to moderate pain and pentazocine 0.3 mg kg^{-1} i.v. for severe pain.

After operation, all episodes of retching and vomiting during the first 24 h after anaesthesia were recorded by nursing staff blinded to the treatment each patient had received. Nausea was not assessed in this study because of the age of the patients. A complete response was defined as no retching, no vomiting and no need for another rescue antiemetic during the first 24 h after anaesthesia. Details of adverse events were recorded by nurses who interviewed the parents of each patient.

Patient data were analysed using one-way analysis of variance (ANOVA), Student's *t* test and chi-square test, where appropriate. The incidence of complete response, retching and vomiting, rescue antiemetic required and adverse events were compared using Fisher's exact probability test. $P<0.05$ was considered significant. All values are expressed as mean (SD) and number (%). Forty patients in each group were sufficient to detect a difference with a=0.05 and power 1–ß=0.8.

Results

Patient characteristics and anaesthesia data are summarized in table 1. There were no significant differences between groups.

There was a complete response in 16 of 40 (40%) patients who had received placebo, in 19 of 40 (48%) of those who had received granisetron 20 μg kg^{-1} (P=0.326), in 34 of 40 (85%) of those who had received granisetron 40 μg kg^{-1} (P=0.001) and in 36 of 40 (90%) of those who had received granisetron 80 μg kg^{-1} (P=0.001) (table 2).

Nine patients who had received placebo and eight of those who had received granisetron 20 μg kg^{-1} required another rescue antiemetic for the treatment of two or more episodes of vomiting, whereas none who had received granisetron 40 or 80 μg kg^{-1} required rescue medication (P=0.001) (table 2).

The most frequently reported adverse events were headache, drowsiness and constipation. There were no differences between the four groups in the number of patients who complained of these symptoms (table 3).

Discussion

We have demonstrated recently that i.v. granisetron reduced the incidence of postoperative emesis in children undergoing tonsillectomy with or without adenoidectomy.[6] However, the fact that granisetron is more expensive than other antiemetics may delay its widespread use. Oral granisetron is less expensive than the i.v. form.[7] Preoperative oral granisetron 40 μg kg^{-1} and 80 μg kg^{-1} provided more effective antiemetic prophylaxis than placebo, but there was no difference in complete response between the placebo and granisetron 20 μg kg^{-1} groups.

The cause of a high incidence of emesis after paediatric tonsillectomy remains unclear, but is probably multifactorial.[2] A number of factors, including age, obesity, history of motion sickness or previous postoperative emesis, operative procedure, anaesthetic technique and postoperative pain are considered to increase the incidence of postoperative vomiting. However, in this study there were no differences between the groups with regard to patient data, surgical procedure, anaesthetics administered and analgesics used after operation, and children with a history of motion sickness or previous emesis were

Table 3 Adverse events (number). No significant differences

	Placebo (n=40)	Granisetron 20 μg kg^{-1} (n=40)	Granisetron 40 μg kg^{-1} (n=40)	Granisetron 80 μg kg^{-1} (n=40)
Headache	2	2	2	2
Drowsiness	1	1	1	1
Constipation	1	1	1	2

excluded. Therefore, the difference in the incidence of complete response between the groups can be attributed to differences in the antiemetics tested.

I.v. granisetron has been shown previously to be effective against emesis induced by cancer chemotherapy[8] and recently in children undergoing tonsillectomy with or without adenoidectomy.[6] Oral granisetron has been shown to be effective in the treatment of chemotherapy-induced emesis.[9] Our study demonstrated that the incidence of complete response in patients who had received oral granisetron 40 and 80 μg kg^{-1} was higher than in those who had received placebo. The exact mechanism of action of granisetron in preventing postoperative emesis remains unclear but it has been suggested that it may act on sites containing 5-HT$_3$ receptors with demonstrated antiemetic effects.[10]

We could find no report on the minimum effective dose of oral granisetron for the prevention of postoperative emesis in children. However, our study demonstrated that the antiemetic efficacy of granisetron 40 μg kg^{-1} was similar to that of granisetron 80 μg kg^{-1}, and also that there were no differences in complete response between placebo and granisetron 20 μg kg^{-1}. This suggests that granisetron 40 μg kg^{-1} may be an effective antiemetic for the prevention of vomiting after paediatric tonsillectomy, and that increasing the dose to 80 μg kg^{-1} provides no demonstrable benefit.

This study also showed that nine of 40 patients who had received placebo and eight of those who had received granisetron 20 μg kg^{-1} required another rescue antiemetic (e.g. domperidone) for the treatment of severe vomiting (i.e. two or more episodes of vomiting), compared with none who had received granisetron 40 or 80 μg kg^{-1} (P=0.001).

The most commonly reported adverse events were headache, drowsiness and constipation. The incidence of these symptoms was comparable between groups. Therefore, oral granisetron may be considered to be relatively free of adverse effects for preventing postoperative emesis in children.

The results of this study are important because of the potential reduction of cost of therapy. In Japan, our hospital pharmacy pays $12.6 for oral granisetron 1 mg (approximately 40 μg kg^{-1}) and $33.4 for granisetron 1 mg i.v. The cost of granisetron is higher than that of other antiemetics, such as droperidol and metoclopramide. However, the use of these antiemetics has been limited because of their undesirable adverse effects, such as excessive sedation and extrapyramidal symptoms.[2]

In summary, we have found that preoperative oral granisetron, in doses greater than 40 μg kg^{-1}, was effective for the prevention of postoperative vomiting in children undergoing tonsillectomy.

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Haemodynamic and electroencephalographic response to insertion of a cuffed oropharyngeal airway: comparison with the laryngeal mask airway

L. Versichelen, M. Struys, E. Crombez, K. Fonck, E. Mortier and G. Rolly

Summary

We have compared the cuffed oropharyngeal airway (COPA), a modified Guedel airway device with a specially designed cuff at its distal end, with the laryngeal mask airway (LMA), on haemodynamic and electroencephalographic (EEG) responses to insertion. In addition, we examined the haemodynamic and EEG changes during initiation of the effect-compartment controlled infusion. We studied 35 female patients undergoing ambulatory gynaecological surgery allocated randomly to received an LMA or COPA to manage the airway. After premedication with midazolam 0.03 mg kg^{-1} i.v. and low-dose alfentanil (0.01 mg kg^{-1}), anaesthesia was induced and maintained with propofol, using an effect-compartment controlled infusion set at an effect-site concentration of 4 μg ml^{-1}. After intercompartmental equilibration, the LMA (group I) or COPA (group II) was inserted and haemodynamic (arterial pressure, heart rate) and EEG (bispectral index (BIS)) responses to insertion studied. The effect-compartment controlled infusion of propofol caused only mild haemodynamic changes during induction. Changes in arterial pressure and heart rate after insertion were similar in both groups and not significantly different from baseline values before insertion. Changes in BIS after insertion were minor and similar between groups. (*Br. J. Anaesth.* 1998; **81**: 393–397).

Keywords: monitoring, bispectral index; equipment, tubes tracheal; cardiovascular system, effects; intubation tracheal; equipment, masks anaesthesia

The use of the laryngeal mask airway (LMA) has become increasingly popular in anaesthesia for maintaining airway patency during spontaneous and controlled ventilation.[1] It has the advantage that it does not require laryngoscopy for insertion. The haemodynamic response to insertion of the LMA is significantly less than after laryngoscopy and tracheal intubation.[2 3] These responses may be harmful in patients with cardiovascular and cerebral disease.

Recently, the cuffed oropharyngeal airway has been introduced into clinical practice as an alternative to the LMA. It consists of an adapted Guedel airway with an inflatable cuff at the distal end and a circuit connection at the proximal end. The COPA is an airway device intended for "hands free" anaesthesia with spontaneous ventilation.[4]

When measuring haemodynamic and EEG responses during anaesthesia, it is important to maintain a comparable adequate depth of anaesthesia during the recording period by maintaining a similar pharmacological state in all patients. A pharmacokinetically based technique for administration of propofol (target-controlled infusion, TCI) can offer adequate and adjustable steady-state conditions.[5] Target-controlled infusions use a computer which, on the basis of pharmacokinetic data,[6] calculates the concentration in plasma or in a theoretical effect-site compartment and adjusts the infusion rate in such a way that a preset concentration is rapidly achieved and maintained.[7 8] Effect-compartment modelling is relevant because of a difference between measured plasma concentrations of the drug and simultaneous indices of drug effect (e.g. the processed EEG). Therefore, it becomes appealing to be able to maintain a constant baseline clinical drug effect using an effect-compartment controlled infusion.

When studying responses to insertion of the COPA or LMA, it is important to observe both haemodynamic and EEG variables. A reduced haemodynamic effect response may be beneficial in patients with cardiovascular and cerebral disease.[9] The stimulus created during insertion of an airway device may cause arousal and changes in the anaesthetic state but haemodynamic responses to stimulus are not adequate measurements of depth of anaesthesia[10 11] and more objective methods should be used. Cerebral responses may be studied by bispectral analysis, a new processed EEG technique. This technique can be a useful measure of anaesthetic drug effect and may be useful as a measure of depth of anaesthesia.[12 13] Compared with classical power spectral analysis which uses the frequency and amplitude of the raw EEG signal to compute a processed univariate parameter,[14] bispectral analysis uses not only complex Fourier transformation but also information on the influence of inter-relations between different components (phase coupling). The bispectral index (BIS) is a single numeric variable between 0 and 100 derived using an algorithm applying bispectral analyses in combination with other EEG features such as the level of burst suppression.[16]

We have measured the haemodynamic and EEG responses to insertion of the COPA in spontaneously breathing, healthy, normotensive patients and

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compared these with insertion of an LMA after theoretical cerebral equilibration using propofol effect-compartment controlled infusion. In addition, haemodynamic and EEG changes during initiation of this infusion were examined.

Patients and methods

After obtaining approval from the Institutional Ethics Committee and informed patient consent, we studied 35 female, ASA I and II patients, undergoing ambulatory gynaecological surgery, allocated randomly to one of two groups. Patients weighing 20% more or less than their ideal weight and those receiving cardiovascular or antihypertensive medications were excluded. Non-invasive arterial pressure, electrocardiogram, peripheral oxygen saturation, end-tidal carbon dioxide and EEG were measured. For haemodynamic data, a Datex AS3 monitor (Datex, Helsinki, Finland) was used and for EEG data, an Aspect A-1000 EEG monitor (Aspect, Natick, USA). Electrodes were placed with montages F7 to reference (Fz) and F8 to reference (Fz), applying the international 10–20 system of electrode placement. Electrode impedance was maintained at less than 5000 Ω to ensure adequate signal quality. Artefacts caused by poor signal quality were detected automatically and excluded from further analysis. BIS (calculated for each 4-s epoch) and its trend were displayed on screen. All data were recorded automatically on computer (Toshiba Satellite Pro 430 CDT, Japan) using self-designed software. BIS data were averaged using 30-s time intervals. For the haemodynamic data, values 1 min before premedication with midazolam were defined as pre-induction baseline. Measurements were also recorded at 3 and 2 min before induction, at induction and thereafter every 1 min until 6 min after induction. Haemodynamic values at 4 min after induction were used as pre-stimulus baseline. For BIS, data before premedication with midazolam were used as pre-induction baseline. All EEG variables were recorded every 4 s until 6 min after induction. BIS at 4 min after induction was used as the pre-stimulus baseline.

Patients were allocated randomly to one of two groups using a randomization table. In group I (n=17), patients were managed using an LMA (TDM, Zaventem, Belgium) (initially size 3 and if necessary size 4) and those in group II (n=18) by a COPA (Mallinckrodt, Hennef, Germany) (initially size 10 and if necessary size 11).

After i.v. cannulation of a large forearm vein, all patients were premedicated with midazolam 0.03 mg kg^{-1} i.v., 5 min before induction. No i.v. volume loading was given before induction. Two minutes before induction, a single i.v. bolus of alfentanil 0.01 mg kg^{-1} was administered. Anaesthesia was induced and maintained with propofol, using Stanpump, a TCI system. The Stanpump program for TCI on a personal computer was used to control a Graseby 3400 syringe pump. Stanpump was written by Steven L. Shafer, MD (Stanford University, Anaesthesiology Service (112A), PAVAMC, 3801 Miranda Ave, Palo Alto, CA 94304, USA) and is freely available from the author. Stanpump controls effect-compartment controlled infusion. The rate constant k_{e0}=0.239 min^{-1}, published by Schüttler, Schwilden and Stoeckel,[16] was used. The software in Stanpump includes a three-compartment pharmacokinetic model, a specific set of pharmacokinetic variables for propofol[6] and algorithms for infusion control. On screen, the anaesthetist can see the desired effect-site concentration and the actual predicted propofol effect-site and plasma concentration during infusion. Before starting Stanpump, individual patient anthropometric data are entered into the computer.

For induction, the target effect-site concentration of propofol was set at 4 μg ml^{-1}. After 4 min, theoretical intercompartmental equilibration was reached between effect-site and plasma. At this moment, the LMA or COPA was inserted. The same anaesthetist inserted all airway devices and assessed ease of insertion on the basis of an established scale.[17] The conditions of insertion were scored as follows: excellent (jaw relaxed, no cough, no diaphragmatic movement, insertion of the device very easy); good (moderate relaxation of the jaw, slight coughing, no movement of diaphragm or limbs, insertion of the LMA possible); poor (moderate jaw relaxation, moderate coughing, movement of diaphragm or limbs, insertion of the LMA difficult); and unable to insert (jaw tightly closed, insertion of the LMA impossible). To minimize a learning effect in the COPA group, because of more experience with the LMA, clinical experience in inserting the COPA was gained in 40 patients in this trial before starting this study.

To study the haemodynamic and EEG response during and after insertion of the COPA or LMA, measurements were recorded until 6 min after induction. It was intended that all patients breathe an oxygen–air mixture spontaneously.

Data are presented as mean (SD) or as individual results. Data were analysed using repeated measures analysis of variance (ANOVA). When statistical significance (P<0.05) was found, the difference for each variable between two different measures was analysed using the Student's two-tailed t test for paired data. Where necessary, Bonferroni correction was applied. Data were compared between groups using a two-sample t test. Categorical data were analysed using Fisher's exact test.

Results

There were no significant differences between groups for weight, age or height. In group I, all patients received an LMA size 3. The LMA was inserted in one attempt in all 17 patients. In group II, 13 patients received a COPA size 10 and five a COPA size 11. The COPA was inserted in 16 of 18 patients in one attempt; in the two other patients a second attempt was necessary. Quality of insertion was compared between groups (table 1).

Table 1 Quality of insertion of the LMA or COPA (see text for details)

	LMA	COPA
Excellent	11/17	13/18
Good	3/17	5/18
Poor	3/17	0/18
Unable	0/17	0/18

Haemodynamic measurements (systolic arterial pressure, diastolic arterial pressure and heart rate) (figs 1–3) were recorded for all patients. Pre-induction (baseline) haemodynamic values were similar in the two groups. After induction of anaesthesia, there was a significant, but clinically moderate, decrease in systolic and diastolic arterial pressures compared with pre-induction baseline. Although values at 3 min after induction were still below pre-induction baseline, systolic and diastolic arterial pressures were stable 3–4 min after induction. The decreases in arterial pressures were similar for both groups until 4 min after induction. There were no changes in heart rate from baseline until 4 min after induction.

After insertion of the LMA (group I) or COPA (group II), we measured maximum changes in systolic and diastolic arterial pressures from pre-stimulus baseline, just before insertion at 4 min after induction. These maximum changes were compared between groups. Changes in systolic arterial pressure were 4 (10) mm Hg in group I and 9 (8) mm Hg in group II (ns between groups). Changes in diastolic arterial pressure were 10 (10) mm Hg in group I and 3 (9) mm Hg in group II ($P<0.05$ between groups). Maximum changes in heart rate after insertion (4–6 min after induction) from pre-stimulus baseline were not statistically significant (group I, 2 (9) beat min^{-1}; group II, 7 (8) beat min^{-1}). Subsequently, there were no significant changes in heart rate between groups.

BIS results from pre-induction baseline until 6 min after induction are shown in figures 4 and 5 for groups I and II, respectively. At 4 min after induction (pre-stimulus baseline), BIS values were 48 (7) and 51 (9) for groups I and II, respectively (ns). BIS response to insertion of the airway device was recorded until 2 min after insertion (4–6 min after induction) and results were compared with pre-stimulus baseline. Maximum changes in BIS response to insertion of the airway device from pre-stimulus baseline were significant for both groups (12 (11) in group I and 15 (10) in group II). Comparison between groups for maximum BIS response was not significant.

Discussion

Laryngoscopy and tracheal intubation during anaesthesia are frequently associated with transient hypertension, tachycardia and arrhythmias.[18] These haemodynamic responses reflect the increase in sympathetic and sympathicoadrenal activity in response to oropharyngeal, laryngeal and tracheal stimulation.[19] The LMA is used widely in airway management.[21 22] Wood and Forrest[3] recommended the use of the LMA as a means of avoiding the haemodynamic response to tracheal intubation in circumstances where such a response might be undesirable.[3] This was also proved by Hollande and colleagues[23] who found no significant changes in heart rate or non-invasive arterial pressure after insertion of the LMA during continuous propofol anaesthesia.

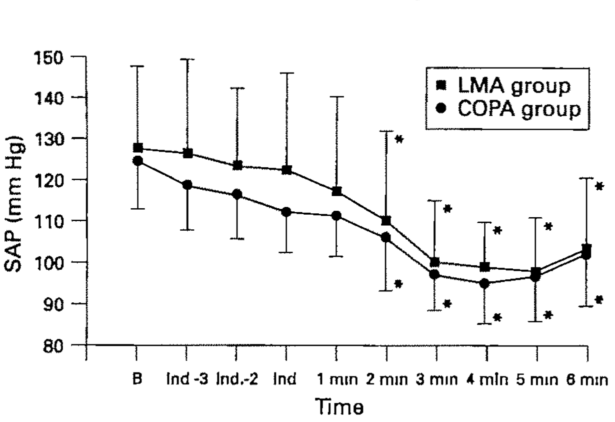

Figure 1 Systolic arterial pressure (SAP) in the LMA and COPA groups measured 3 (Ind.-3) and 2 (Ind.-2) min before induction (Ind.), and every 1 min for 6 min after induction. *$P<0.05$ compared with pre-induction baseline (B).

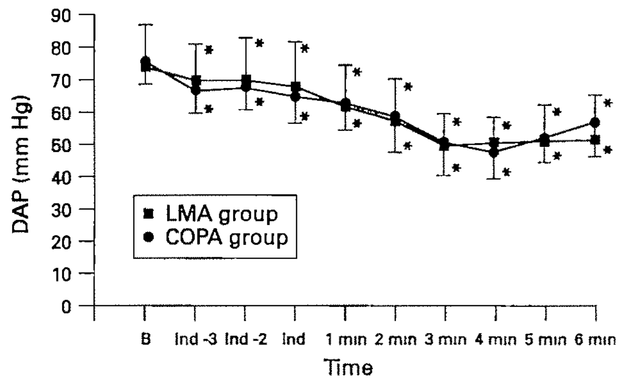

Figure 2 Diastolic arterial pressure (DAP) in the LMA and COPA groups measured 3 (Ind.-3) and 2 (Ind.-2) min before induction (Ind.), and every 1 min for 6 min after induction *$P<0.05$ compared with pre-induction baseline (B).

The recently developed COPA device is inserted in the mouth of the patient facing the hard palate and then turned 180° to rest finally in position with the ventral surface along the tongue and the dorsal surface along the pre-vertebral mucosa of the pharynx, similar to insertion of a Guedel airway. It can effectively support the airway in spontaneously breathing anaesthetized patients[4] and oropharyngeal and laryngeal stimulation may be less with insertion of the COPA than with the LMA. The aim of this study was to compare the COPA with the LMA and to measure the haemodynamic and EEG responses to insertion of these devices in spontaneously breathing, healthy, normotensive patients.

We found minor haemodynamic changes in the LMA group but these were not statistically significant. Similar results were found in the COPA group. Although insertion of the laryngeal mask was qualitatively less successful than insertion of the COPA (table 2), this did not result in greater haemodynamic changes.

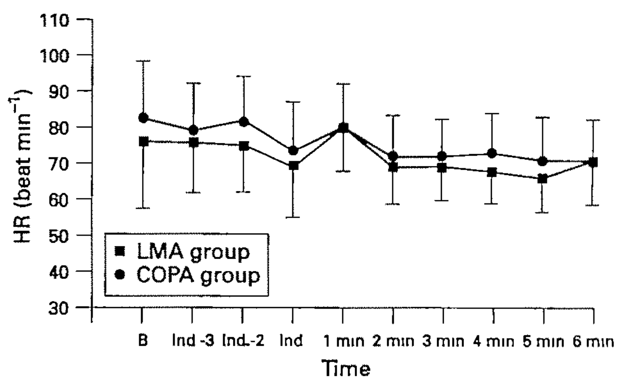

Figure 3 Heart rate (HR) in the LMA and COPA groups measured 3 (Ind.-3) and 2 (Ind.-2) min before induction (Ind.), and every 1 min for 6 min after induction. B=Baseline

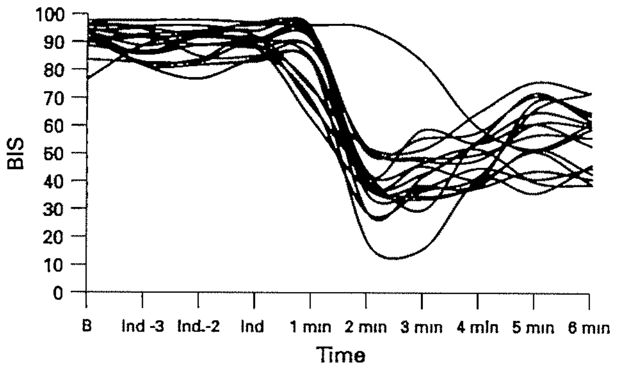

Figure 4 Bispectral index (BIS): individual data from the LMA group (averaged using 30-s time intervals) measured 3 (Ind.-3) and 2 (Ind.-2) min before induction (Ind.), and every 1 min for 6 min after induction.

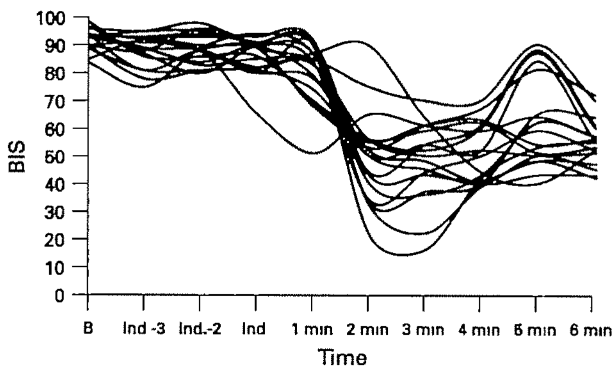

Figure 5 Bispectral index (BIS): individual data from the COPA group (averaged using 30-s time intervals) measured 3 (Ind.-3) and 2 (Ind.-2) min before induction (Ind.), and every 1 min for 6 min after induction.

Differences in arousal level between insertion of different devices are of interest. Haemodynamic changes are adequate for measuring the sympathetic response to stimulus but are ineffective for studying changes in hypnotic level.[10 11] Therefore, BIS was used to monitor changes in depth of anaesthesia after insertion of the LMA or COPA. Bloom, Greenwald and Day have shown that BIS reacts to arousal caused by stimulus, and this reaction is less when higher doses of analgesics are used.[24]

The level of depth of anaesthesia is important when measuring haemodynamic changes. The sympathetic response to stimulus may increase significantly more when the level of anaesthesia is insufficient. Therefore, we used an intercompartmental equilibrated concentration of propofol 4 $\mu g\ ml^{-1}$ combined with low-dose alfentanil to provide adequate and comparable depths of anaesthesia. Cerebral effects were also measured using BIS which showed adequate levels of anaesthesia of approximately 50 before insertion of the airway device. In a previous study, we found that a combination of an effect-site controlled infusion of propofol and a BIS of 40–60 provided an adequate level of anaesthesia.[13]

Acalovschi, Miclescu and Bugov[17] studied the effects of the induction agent (propofol or thiopental) on laryngeal reactivity and haemodynamic response to LMA insertion, and concluded that insertion conditions were better after induction with a propofol bolus dose compared with thiopental. Propofol also prevented the cardiovascular effects of insertion of the LMA more effectively. In our study, pre-stimulus depth of anaesthesia was adequate because BIS in all patients was within the limits of normal anaesthetic depth.[25]

We obtained pharmacologically comparable circumstances before stimulus by administering the same doses of propofol and alfentanil. Changes in BIS in both groups showed a similar response to insertion of the LMA or COPA. BIS values increased significantly compared with pre-stimulus baseline, but differences between groups were minor. Therefore, propofol 4 $\mu g\ ml^{-1}$ combined with alfentanil 0.01 $mg\ kg^{-1}$ provided adequate conditions for insertion of the LMA or COPA. As shown in figures 4 and 5, premedication with midazolam did not affect BIS.

In addition, the changes in haemodynamic state and BIS during effect-compartment controlled infusion of propofol to an effect-site concentration of 4 $\mu g\ ml^{-1}$ were recorded. Many anaesthetists hesitate to use this infusion technique because of the fear that side effects may be more pronounced with infusions directed to a preset effect-site concentration than with infusions directed to a preset plasma concentration. This could happen if effect-sites responsible for the cardiovascular side effects equilibrated faster with plasma concentrations than those responsible for cerebral (anaesthetic) effects, thus reaching higher values because of the overshoot in plasma concentration associated with effect-compartment controlled infusions. However, there is little or no documentation supporting this. In this respect, the results of our study are encouraging in that cardiovascular effects during the first minutes of infusion were relatively mild and the rate of change of the cardiovascular effects appeared to be slower than that of the cerebral effect. This needs to be explored further in future research.

In summary, we compared the COPA with the LMA and measured the haemodynamic and cerebral responses to insertion of these devices in spontaneous breathing, healthy, normotensive patients. There were no significant differences in haemodynamic state for both devices compared with baseline values. A minor cerebral response, measured by BIS, was noted in both groups. There were no differences in haemodynamic or cerebral responses between devices. Regarding stimulus on insertion, the COPA was a valuable, but no better, alternative to the LMA.

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British Journal of Anaesthesia 1998; **81**: 398–400

Saline as an alternative to air for filling the laryngeal mask airway cuff

A. COOREY, J. BRIMACOMBE AND C. KELLER

Summary

We have assessed a new method to evacuate saline completely from the laryngeal mask airway (LMA) cuff and tested the hypothesis that intracuff pressures, fibreoptic position and oropharyngeal leak pressures are similar for saline compared with air during nitrous oxide–oxygen anaesthesia. Eight size 4 LMA were inflated with saline 30 ml. After syringe evacuation, median residual weight was 0.56 (range 0.24–0.98) g; after additional manual cuff squeezing it was 0.26 (0.21–0.35) g; and after drying for 12 h at 60°C with the valve open it was –0.02 (–0.05–0.04) g. Pressure–volume curves of four size 3–5 LMA showed that compliance was lower for the saline-filled cuff. A clinical study of 20 patients allocated randomly to have saline or air in the cuff showed a significant increase in intracuff pressure with air, but not saline, during nitrous oxide–oxygen anaesthesia. The fibreoptic position of the LMA changed more frequently in the air, compared with the saline-filled group (four of 10 *vs* none of 10; P=0.04). Oropharyngeal leak pressures were similar between groups. We conclude that the saline-inflated LMA cuff was reliably emptied and more stable in terms of intracuff pressures and possibly fibreoptic position. Filling the LMA cuff with saline is a viable option during laser surgery to the airway. (*Br. J. Anaesth.* 1998; **81**: 398–400).

Keywords: equipment, masks anaesthesia; intubation tracheal; surgery, laser

The laryngeal mask airway (LMA) has been used during laser surgery to the upper[1] and lower airways.[2, 3] A well documented hazard of laser surgery is the risk of airway fires. Although the LMA is relatively laser resistant, it can be ignited at clinically used power densities and the cuff represents the most significant fire risk.[4, 5] A recent study demonstrated that ignition was less likely if saline was used as an alternative to air for cuff inflation,[4] as recommended for tracheal tube cuffs.[6] However, inflating the cuff with saline puts the device at risk during autoclave sterilization from expansion of any residual fluid,[7] and the clinical effects of using saline as the cuff filling agent are unknown. In this study we assessed a method of evacuating saline completely from the LMA cuff and tested the hypothesis that intracuff pressures, fibreoptic position and oropharyngeal leak pressures are similar for saline compared with air during nitrous oxide–oxygen anaesthesia.

Patients and methods

Four size 4 LMA were inflated with saline 30 ml and then emptied via a syringe with the cuff held above the syringe to facilitate gravitational drainage. A syringe without plunger was inserted into the valve to keep it open and the cuff squeezed manually. The LMA with syringe barrel attached was then placed in a warming cupboard at 60°C for 12 h. The LMA was weighed using a Sartorius electronic scale: before filling (cuff evacuated to –40 mm Hg); when full; after initial emptying; after manual squeezing; and after drying. This experiment was performed twice on each LMA. Pressure–volume relationships were also obtained for sizes 3, 4 and 5 LMA: four LMA for each size were inflated with air and then with saline in 5-ml increments. Intracuff pressure was measured using a calibrated pressure transducer. All LMA were in routine clinical use, had been through at least 20 autoclave cycles and had passed the pre-use check tests.

We studied 20 ASA I–II adult patients undergoing routine peripheral surgery in the supine position, allocated randomly to either air or saline as the cuff-filling agent. LMA size was determined by height (≥165 cm, size 5; <165 cm, size 4). Approval was obtained from the Ethics Committee and all patients gave written informed consent. A standard anaesthesia procedure was followed. All LMA had been autoclaved at least 20 times before the start of the study; this is well beyond the phase of greatest compliance change as a result of age.[7] Patients were preoxygenated and anaesthesia was induced with fentanyl 1 μg kg^{-1}, midazolam 0.025 mg kg^{-1} and propofol 2.5 mg kg^{-1}. Neuromuscular block was achieved with atracurium 0.5 mg kg^{-1} and initial maintenance of anaesthesia with 1–2% isoflurane in oxygen. A pressure transducer (as above) was zeroed at the level of the external auditory meatus and connected to an LMA via a three-way tap. A single LMA user (A. C.), using the standard recommended technique, inserted the LMA.[8] The cuff was inflated to a pressure of approximately 45 mm Hg and the device fixed in position, as recommended by the manufacturer.[8] An oropharyngeal leak test was performed by closing the expiratory valve of the circle system at a fixed gas flow of 3 litre min^{-1} and noting the airway

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Table 1 Calculated weight of saline (g) in the four size 4 LMA (two measurements each device) at the following times: injected, after syringe evacuation, manual squeezing and drying

	LMA 1		LMA 2		LMA 3		LMA 4	
Injected	35.00	30.19	30.71	30 04	30.09	30.57	30.26	28.99
After syringe evacuation	0.96	0.98	0.36	0.93	0.31	0 33	0.35	0 24
After manual squeezing	0.26	0.29	0.25	0.35	0 24	0 27	0 21	0 21
After drying	0.04	–0.02	–0 05	–0.03	–0.01	–0.03	–0.02	–0.03

pressure at which gas leak occurred into the mouth (oropharyngeal leak pressure).[9 10] The view of the cords was scored fibreoptically using an established scoring system.[11] Nitrous oxide 66% was added to the anaesthetic mixture. Patients underwent positive pressure ventilation with peak airway pressure ≤15 cm H_2O. Intracuff pressures were measured at 5-min intervals for 25 min. Oropharyngeal leak pressure and fibreoptic score were reassessed at 25 min (before neuromuscular block was antagonized). Patients were questioned about sore throat on the first day after operation. A trained investigator (A. C.) performed all observations.

Observer consistency/accuracy for subjective assessments (oropharyngeal leak tests and fibreoptic scoring) was verified before the start of the study by comparison with the second investigator (J. B.). Sample size was selected to detect a projected difference of 25% between groups for a type I error of 0.05 and a power of 0.8. Statistical analysis was with the Student's *t* test, Fisher's exact test and repeated measures analysis of variance. Unless otherwise noted, data are presented as mean (SD) or median (range). Significance was taken as $P<0.05$.

Results

Median mass of saline used to inflate the cuff was 30.7 (28.99–35.00) g. The residual weight after syringe evacuation was 0.56 (0.24–0.98) g, after manual squeezing 0.26 (0.21–0.35) g and after drying –0.02 (–0.05–0.04) g (table 1). The pressure–volume curves for the size 3, 4 and 5 LMA are shown in figure 1. Compliance was significantly lower for the saline-filled cuff compared with the air-filled cuff when cuff volume exceeded 36 ml for the size 5, 24 ml for the size 4 and 18 ml for the size 3 LMA.

There were no failed LMA insertions and ventilation was effective in all patients. There were differences in patient characteristics between the groups (table 2). Initial intracuff pressures between the air-filled group and saline group were similar. Intracuff pressure was significantly different over time in the air group ($P<0.0001$), but not in the saline group ($P=0.12$). Intracuff pressures in the air group increased progressively with time compared with the saline group, the difference becoming significant after 15 min (fig. 2). Initial cuff volume, intracuff pressure, oropharyngeal leak pressure and fibreoptic scores were similar between groups. Oropharyngeal leak pressures were similar within groups initially and at 25 min. Fibreoptic scores initially and at 25 min were similar within the saline group, but were significantly different within the air group ($P=0.04$). In the air group, the fibreoptic view improved in one patient and deteriorated in three patients. No patient had a sore throat.

Table 2 Patient characteristics, LMA size, oropharyngeal leak pressure (OPL) and fibreoptic scoring for each group (mean (SD or range) or number). Fibreoptic score: 4=only vocal cords visible, 3=vocal cords and posterior epiglottis, 2=vocal cords and anterior epiglottis, 1=vocal cords not seen[11]

	Air-filled	Saline-filled
Age (yr)	42 (23–64)	32 (18–66)
Height (cm)	171 (8)	171 (5)
Weight (kg)	77 (13)	85 (19)
Sex (M:F)	6:4	6 4
ASA I/II	7/3	6/4
Mallampati grade 1/2/3	5/2/3	5/4/1
LMA size 4/5	4/6	1/9
Initial OLP (cm H_2O)	22 (6)	23 (4)
Final OLP (cm H_2O)	25 (6)	26 (5)
Initial fibreoptic score 4/3/2/1	1/2/5/2	2/0/6/2
Final fibreoptic score 4/3/2/1	1/1/5/3	2/0/6/2

Discussion

Our data showed that the saline-inflated LMA cuff was reliably emptied if the described technique was followed. Asai, Koga and Morris demonstrated that

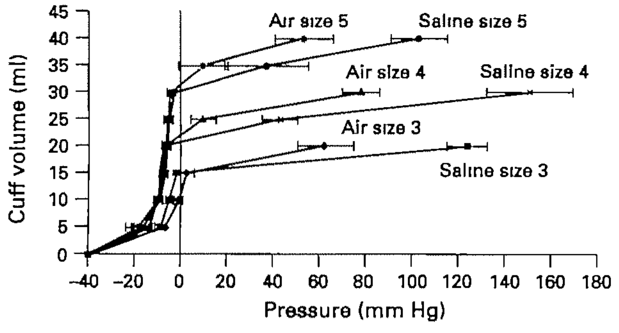

Figure 1 Pressure–volume relationship curves for the sizes 3, 4 and 5 LMA using saline or air as the filling agent. Data are mean (SD).

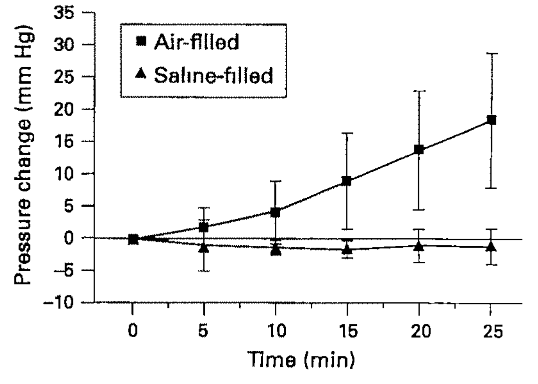

Figure 2 Intracuff pressures during nitrous oxide–oxygen anaesthesia using saline or air as the filling agent. Data are mean (SD).

water 0.25 ml could damage the cuff after repeat autoclaving.[7] After syringe evacuation and manual squeezing, there is still more than 0.25 g of residual saline in the cuff and it is therefore essential that the cuff be dried to prevent structural damage during autoclaving. This technique could also be used to remove any fluid accidentally introduced into the cuff or to flush out other contaminants. The residual volume of air in the deflated size 4 LMA is 0.6–2.0 ml depending on the degree of evacuation.[12 13] Any residual air contains a small amount of moisture and this may explain why the weight after drying was less than the pre-inflation weight (approximately −20 mg). The greater density and low compressibility of saline compared with air explain the lower compliance of the saline-filled cuff.

Our data also showed that the LMA has more stable intracuff pressures and fibreoptic position when saline is used for inflation. The clinical importance of this is unknown, but it suggests that saline may be a useful filling agent for routine use. Nitrous oxide is known to diffuse into the air-filled LMA cuff and to produce a rapid increase in pressure during nitrous oxide anaesthesia that plateaus at 1–2 h.[14] It is difficult to stabilize cuff pressure during nitrous oxide anaesthesia without repeatedly withdrawing air. A commercially available device is available which, when attached to the pilot valve, maintains pressures at any set value. Inflating the LMA with a nitrous oxide–oxygen mixture is not a reliable method of stabilizing cuff pressures.[15] Fibreoptic positional changes in the air-filled group may be related to increases in cuff volume, but a previous larger study did not reveal any fibreoptic positional changes during prolonged nitrous oxide–oxygen anaesthesia.[14] Differences between studies may be related to variations in cuff volume, accuracy of placement or loss of pharyngeal tone with muscle relaxation. Fibreoptic scoring of LMA position and oropharyngeal leak measurements are subjective and this is a potential weakness of this and other similar studies.[9 10]

It has been shown that there is inter-observer variation when performing a tracheal tube leak test. We aimed to maximize objectivity by using only one trained investigator.[16] Future studies may benefit from the use of photographic records in assessing fibreoptic score. There is some evidence that the use of low intracuff pressures may reduce the incidence of postoperative pharyngolaryngeal morbidity,[17] but this is probably dependent on the initial pressure rather than pressure increase changes. It has been shown that mucosal pressures remain stable despite increases in intracuff pressure.[18]

We conclude that the saline-inflated LMA cuff was reliably emptied and that saline-filled cuffs were more stable in terms of intracuff pressures and possibly fibreoptic position. Filling the LMA cuff with saline is a viable option for laser surgery to the airway.

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British Journal of Anaesthesia 1998; **81**: 401–403

Technique training: endoscopic percutaneous tracheostomy

Q. Gardiner, P. S. White, D. Carson, A. Shearer, F. Frizelle and P. Dunkley

Summary

Percutaneous tracheostomy is being used increasingly in the intensive care unit and endoscopic control of this procedure affords an improved level of safety. Training in such new minimal access techniques can be a significant risk factor in patient outcome. Surgical simulation provides training which minimizes this risk. We present a method of training in percutaneous endoscopic tracheostomy using a simulation model based on animal tissue. Our experience with this model is reported. (*Br. J. Anaesth.* 1998; **81**: 401–403).

Keywords: surgery, endoscopy, surgery, tracheostomy; model, simulation; anaesthetist, training

Various methods of percutaneous tracheostomy have been described.[1 2] Some authors have recommended that some techniques should be "relegated to the wastepile"[3] because of unacceptable levels of operative complications. Longer term complications such as subglottic stenosis have also been reported.[4] Improvement in safety has been demonstrated by carrying out the procedure under bronchoscopic control.[5]

Acquisition of new skills, such as percutaneous endoscopic tracheostomy, requires both supervised training and the opportunity for sufficient practice. It is ethically unacceptable for surgical skills training to be a serious risk factor in patient outcome.[6] Surgical simulations offer a means of achieving these aims without placing patients at risk.[7] In this way a minimum skill level for trainees can be attained before the first live procedure is ever performed.

We present an animal tissue model that allows four to six endoscopically controlled percutaneous tracheostomies to be performed under continuous guidance by a trainer. This facilitates a basic grounding before the procedure is carried out on live patients.

Materials and methods

We studied the laryngobronchial tree of commonly slaughtered agricultural animals and found the pig to be the most suitable. The anatomy of the pig larynx and trachea is remarkably similar to the human. The diameter of the trachea is the same, allowing the standard percutaneous tracheostomy kit and tracheostomy tubes to be used.

The pig thorax is positioned on its back with the head extended, as would be done for a human patient undergoing the same procedure. The animal's trachea is intubated with an oral tracheal tube, the cuff inflated and placed against the glottis creating a seal (fig. 1). A ventilator may be attached to further simulate the real situation. A fibreoptic bronchoscope is passed down the tracheal tube to see the trachea, and a television camera and monitor attached to it. This allows both the trainee performing the procedure to see the results of their manipulations and the trainer to monitor and advise as they proceed (fig. 2). By working from the sternal notch upwards towards the larynx, 4–6 tracheostomies may be performed on each animal tissue preparation.

Both of the two popular percutaneous tracheostomy techniques, the Ciaglia dilational technique and the Portex forceps technique, may be practised on the model. In this way trainees gain a feeling for the technique they prefer. The skill training achieved using the model is rated well by trainees (table 1).

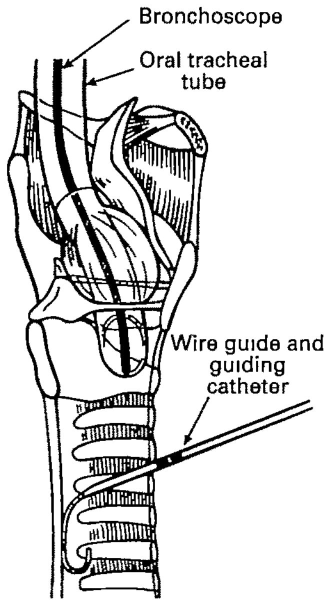

Figure 1 The larynx and upper trachea, showing the position of the oral tracheal tube The seeker needle has been removed and the guide catheter inserted over the guidewire under vision via the bronchoscope.

Q Gardiner, frcs, P S. White, fracs, frcs (Department of Otolaryngology); D Carson, frca, A. Shearer, ffarcs (Department of Anaesthetics); F. Frizelle, fracs, P Dunkley, frcs (Surgical Skills Unit); University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY. Accepted for publication April 2, 1998.

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This article is accompanied by Editorial I

Table 1 "How useful did you find each procedure in learning this technique". (Score between 0 (not useful) and 5 (very useful))

Trainees (n=20)	Mean score
Ciaglia dilatation technique with pig model	4.6
Portex forceps technique with pig model	4.5

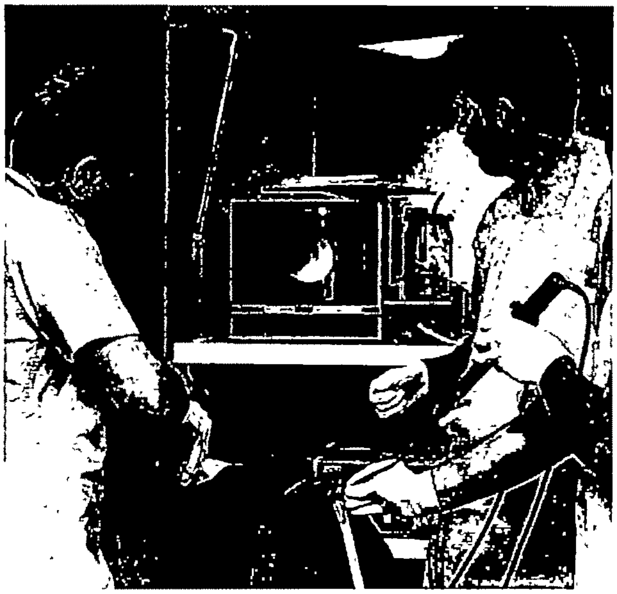

Figure 2 The pig model, with the bronchoscope and monitor in use.

USE OF THE MODEL

First, the fibreoptic bronchoscope is inserted into the tracheal tube and focused correctly so that a good picture is obtained on the monitor screen. The picture obtained is orientated correctly using both the marks on the tracheal tube and the curve of the anterior tracheal wall. The bronchoscope is passed down the trachea to the carina, and the right and left bronchi examined to exclude mucus plugs or other obstructions to ventilation. If these are discovered they may be cleared by suction. The bronchoscope is drawn back to lie just inside the tracheal tube to avoid damage. The sternal notch is palpated and the index finger moved superiorly to lie over the trachea. Pressure is exerted down onto the trachea, and compression of the correct part of the trachea confirmed endoscopically. To maximize the number of insertions practised on each model, the first puncture is initiated at the most inferior available portion of trachea. Subsequent tracheostomies are performed moving cranially in sequence. A 2-cm incision is made in the overlying area of satisfactory compression. The seeker needle is inserted and pressed against the anterior face of the trachea. If this compression is found not to be at a 12 o'clock position, the needle may be "walked" over the trachea until the correct insertion point is determined. In the human situation this allows the level of insertion to be checked; the tracheal rings can be counted until the space between the second and third rings is found. The seeker needle may then be pushed through the tracheal wall into the lumen, and its position confirmed endoscopically.

Insertion of the guidewire follows, and confirmation that it is passing down into the trachea, rather than up into the larynx, is again obtained endoscopically. The initial dilator is slid over the guidewire and the tip manipulated gently until it is seen within the trachea on the monitor: full insertion may then proceed without risk of kinking the guidewire and creation of a false passage.[3]

If a Ciaglia dilation technique is to be used, each bougie insertion is monitored carefully to ensure that there is no damage to the posterior tracheal wall, and that each bougie lies within the tracheal lumen (fig. 3). Using the Portex technique, the same endoscopic control is used to ensure that the forceps are well clear of the posterior tracheal wall. When a sufficiently large fistula has been created in the trachea, the tracheostomy tube may be inserted. Again, endoscopic control ensures that both the tracheostomy tube itself and the cuff of the tube are inserted within the lumen of the trachea. Before the cuff of the tracheostomy tube is inflated, the pig model (or human patient) should remain ventilated adequately via the oral tracheal tube. The final procedure is to pass the bronchoscope through the tracheostomy tube to confirm that it is within the lumen of the trachea, and above the carina. Only then is the tracheostomy tube inflated, the ventilator attached to the tracheostomy tube and the tube sutured into position.

Discussion

Endoscopic control during percutaneous tracheostomy makes the procedure easier and safer to perform. The exact technique we use on our patients and in training on our model differs slightly from the standard protocol. As subglottic stenosis has been reported with tracheal puncture immediately below the cricoid,[4] we have practised insertion between the second and third tracheal rings. When using the non-endoscopic technique it is much easier to place the tracheostomy tube in the subcricoid area, as this is the most superficial.

Using endoscopic control, the level most appropriate for tracheostomy tube insertion can be located without difficulty. We believe that it is not appropriate that such a procedure should be performed for the first time on a patient without prior practice using a simulation. The reckless use of the non-endoscopic

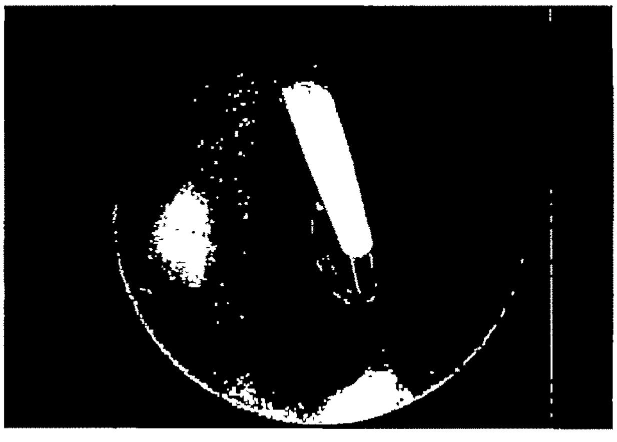

Figure 3 An endoscopic view of the Ciaglia dilator being inserted into the trachea of the model.

procedure without proper training inevitably leads to complications and possible unnecessary fatalities.

We have presented a model which simulates the human trachea well and allows monitoring of skill acquisition. Practical training using models is a well proven method of teaching new techniques safely and is popular with trainees.[8] Mistakes made using the model have no consequences in terms of patient care: those on live patients may be disastrous.

Acknowledgements

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British Journal of Anaesthesia 1998; 81: 404–408

LABORATORY INVESTIGATIONS

Evaluation of nitrogen dioxide scavengers during delivery of inhaled nitric oxide

L. LINDBERG AND G. RYDGREN

Summary

We have analysed the ability of three nitrogen dioxide absorbing materials (soda lime, noXon and zeolite) to act as nitrogen dioxide scavengers during delivery of inhaled nitric oxide. Different mixtures of gas were produced in a ventilator (Servo Ventilator 300) and passed through an inspiratory tube. Concentrations of nitrogen dioxide and nitric oxide were measured in the distal part of the tube, with and without the gas having passed through a canister containing the different filter materials. Our findings indicated that nitrogen dioxide was absorbed effectively by all filter materials but that there was re-formation of nitrogen dioxide from nitric oxide and oxygen in or immediately after the canister. This initial production of nitrogen dioxide was very rapid and could not be prevented by the use of scavengers. Thus soda lime and zeolite had no practical effect as scavengers in this delivery system, and the effect of noXon was very slight. (*Br. J. Anaesth.* 1998; **81**: 404–408)

Keywords: pharmacology, nitric oxide; gases non-anaesthetic, nitric oxide; gases non-anaesthetic, nitrogen dioxide; ventilation, mechanical; equipment, scavenging devices

Inhalation of nitric oxide has been shown to reduce pulmonary artery hypertension and improve oxygenation in patients with acute lung injury. However, inhaled nitric oxide is potentially toxic because of its rapid oxidation to nitrogen dioxide. Nitrogen dioxide reacts with water to form nitric and nitrous acids which can cause lung injury.[1 2]

The amount of nitrogen dioxide formed during inhalation of nitric oxide depends on the concentrations of oxygen and nitric oxide, and the contact time between the two.[3] In order to decrease the concentration of nitrogen dioxide in the inspired gas, it has been recommended that the concentration of inhaled nitric oxide and oxygen be minimized,[4 5] the time of contact between them reduced as much as possible[6] and the concentration of nitric oxide be kept constant throughout the inspiratory phase.[7] It has also been claimed that the concentration of inspired nitrogen dioxide can be decreased by the use of nitrogen dioxide-absorbing materials, but the value of such scavengers is a matter of debate.[8]

In this study, we have determined the value of three different materials in absorbing nitrogen dioxide in a system for delivery of inhaled nitric oxide.

Methods

Figure 1 shows the experimental layout for administering and measuring concentrations of nitric oxide and nitrogen dioxide.

A Servo Ventilator 300 (Siemens-Elema AB, Solna, Sweden) with a gas module delivering nitric oxide from a stock gas tank of nitric oxide–nitrogen was used to supply different mixtures of nitric oxide and oxygen. A gas flow regulating valve, built on the same gas regulating principle as oxygen and air valves, injects nitric oxide into the inspiratory limb. All three valves are microprocessor-controlled to provide a flow that is rapidly adjusted (ms) in proportion to the main ventilatory flow (flow proportional). This regulatory system maintains the concentration of nitric oxide almost constant during inspiration and expiration, despite changes in minute ventilation, oxygen concentration, mode of ventilation (pressure-regulated, volume-regulated), inspiratory time, pause time, frequency, etc.[9]

A paediatric silicon tube, 0.85 m in length, attached to the ventilator and a canister (diameter 0.07 m, height 0.075 m, volume 290 ml) containing the nitrogen dioxide absorbing material, was connected to the tube by an adapter. The same canister was used for all three materials to minimize differences in volume-dependent absorption and to standardize the deadspace volume on each side of the canister during the tests.

Concentrations of nitric oxide and nitrogen dioxide were measured using electrochemical fuel cells (CiTiceLs, City Technology Ltd, City Technology Centre, Portsmouth, UK) and a chemiluminescence analyser (ML 9841A Monitor Laboratories, LS Lear Siegler, Measurement Controls Corporation, Englewood, CO, USA) after the tube and canister. To avoid contamination with room air, we added a 0.85-m tube after the monitors, and the system was open to atmospheric air to avoid pressure dependency (fig. 1). Two measuring techniques were used to avoid systematic error, but the values obtained with the electrochemical fuel cells were used in the tables and figures.

The chemiluminescence analyser and electrochemical fuel cells were calibrated with dry calibration gas containing nitric oxide (82.2 ppm 2%) and nitrogen dioxide (6.7 ppm 2%) in nitrogen (AGA

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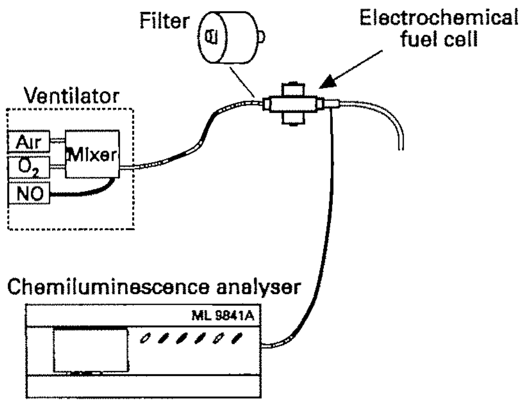

Figure 1 Experimental system for measuring absorption of nitrogen dioxide and transformation of nitrogen dioxide to nitric oxide by three different filter materials.

AB, Lidingö, Sweden). The chemiluminescence analyser is zeroed automatically. The electrochemical fuel cells were zeroed with dry air. The system was flushed with nitric oxide–nitrogen four times to eliminate interference from nitrogen dioxide formed and trapped in the high pressure tubing.

Three types of nitrogen dioxide absorbing materials were studied: (i) soda lime (Viosorb, MIE, Medical and Industrial Equipment, Falcon Road, Souton Industrial Estate, Exeter, Devon, UK) which has a variable undetermined grain size and a density of 0.82 g ml^{-1}. The colour indicator used was ethyl violet; (ii) noXon (Hoechst AG, Frankfurt, Germany), which contains a polymeric material (polyphenylensulphide), has a grain size of 0.7–2 mm and a density of 0.4 g ml^{-1}; (iii) Zeolite 518, 4 Angstrom (Grace, Worms, Germany), a naturally occurring and synthetic group of minerals with a framework consisting of interlocking tetrahedrons of SiO_4 and AlO_4. It has a grain size of 1 mm and a density of 0.78 g ml^{-1}.

In the first series of experiments the ventilator was set to deliver nitric oxide 40, 70 and 100 ppm at an FI_{O_2} of 0.9. The gas source was a high pressure cylinder (160 bars) of nitric oxide in nitrogen (1001±20 ppm) (AGA AB, Lidingö, Sweden). A low minute volume (1 litre min^{-1}) was used to provide the highest possible nitrogen dioxide production. In the second series of experiments the nitric oxide–nitrogen stock gas cylinder was exchanged for a calibration gas cylinder containing nitrogen dioxide–nitrogen 196 ppm (Air Liquide Gas AB, France). This cylinder was connected to the nitric oxide valve which was set to deliver nitrogen dioxide 10 ppm at an FI_{O_2} of 0.21.

Nitric oxide and nitrogen dioxide concentrations were measured during the experiments with and without the canister in place.

The production of nitrogen dioxide was calculated according to the following equation, which describes the concentration of nitrogen dioxide in the delivery system:

$$[NO_2] = k_A \times [NO] + k_B \times [NO]^2 \times [O_2] + k_C \times t \times [NO]^2 \times [O_2]$$

where nitrogen dioxide $[NO_2]$ and nitric oxide [NO] concentrations are in parts per million (ppm), oxygen concentration $[O_2]$ is in percentage, and contact time (t) is in seconds. The rate constants are $k_A=5.12\times10^{-3}$, $k_B=1.41\times10^{-6}$ and $k_C=0.86\times10^{-6}$. Contact time of nitric oxide and oxygen was calculated by dividing the volume of the paediatric tube and adapter by mean gas flow. The calculated values are given in figure 2 A–C, showing the expected approximate concentration of nitrogen dioxide at different concentrations of nitric oxide in the delivery system without a filter.

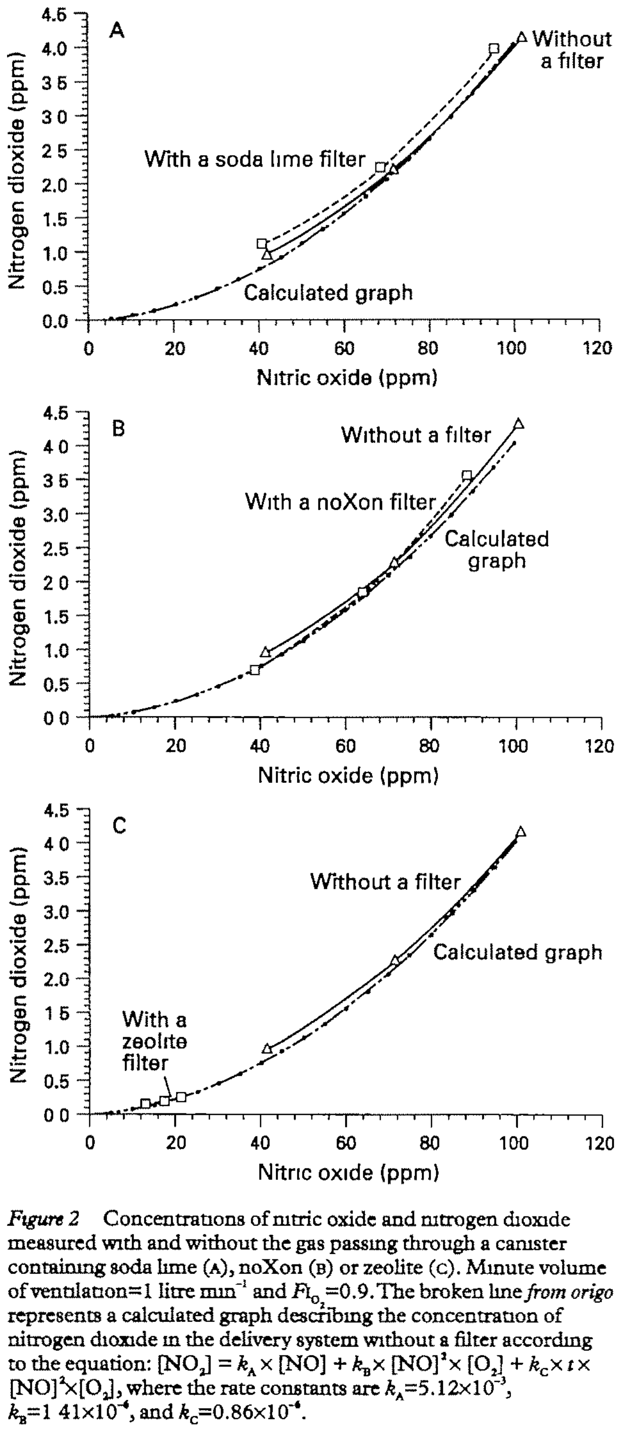

Figure 2 Concentrations of nitric oxide and nitrogen dioxide measured with and without the gas passing through a canister containing soda lime (A), noXon (B) or zeolite (C). Minute volume of ventilation=1 litre min^{-1} and FI_{O_2}=0.9. The broken line *from origo* represents a calculated graph describing the concentration of nitrogen dioxide in the delivery system without a filter according to the equation: $[NO_2] = k_A \times [NO] + k_B \times [NO]^2 \times [O_2] + k_C \times t \times [NO]^2 \times [O_2]$, where the rate constants are $k_A=5.12\times10^{-3}$, $k_B=1.41\times10^{-6}$, and $k_C=0.86\times10^{-6}$.

Absorption of nitrogen dioxide (concentration of nitrogen dioxide before (without) the filter–concentration of nitrogen dioxide after the filter, divided by the concentration of nitrogen dioxide before the filter) and transformation of nitrogen dioxide to nitric oxide (concentration of nitric oxide after the filter–concentration of nitric oxide before (without) the filter divided by concentration of nitrogen dioxide before (without) the filter) were calculated when nitrogen dioxide–nitrogen was delivered and expressed as a percentage.

Results

ABSORPTION OF NITROGEN DIOXIDE IN NITROGEN

All three materials absorbed nitrogen dioxide effectively. Zeolite absorbed almost all nitrogen dioxide (table 1).

TRANSFORMATION OF NITROGEN DIOXIDE TO NITRIC OXIDE

NoXon was the only material that transformed nitrogen dioxide to nitric oxide (table 2).

ABSORPTION OF NITROGEN DIOXIDE PRODUCED BY OXIDATION OF NITRIC OXIDE

Soda lime decreased the concentration of nitric oxide by 6.6% and of nitrogen dioxide by 4.9% at the highest nitric oxide concentration. Concentrations of nitrogen dioxide were always higher with soda lime than without, at comparable concentrations of delivered nitric oxide (fig. 2A).

NoXon decreased the concentration of nitric oxide by 12.1% and of nitrogen dioxide by 17.5% at the highest nitric oxide concentration, but the concentration of nitrogen dioxide was still higher with noXon than without, at comparable concentrations of nitric oxide. At set concentrations of nitric oxide 40 and 70 ppm, concentrations of nitrogen dioxide were reduced by noXon at comparable concentrations of delivered nitric oxide (fig. 2B).

Zeolite decreased the concentration of nitric oxide by 70–80% and nitrogen dioxide by 84–94% (fig. 2C).

Discussion

One of the problems with administration of nitric oxide is spontaneous and continuous oxidation of nitric oxide to the more toxic nitrogen dioxide. Nitrogen dioxide scavengers can reduce the concentration of nitrogen dioxide in inspired gas and it has been recommended that they should be used during inhalation of nitric oxide. Soda lime has been tested by several authors with variable results.[10–13] Our study supports and explains the finding that nitrogen dioxide scavengers have a limited role to play.

Table 1 Absorption of nitrogen dioxide (NO_2/N_2) by the three different filter materials

	NO_2 without absorber (ppm)	NO_2 after absorber (ppm)	Absorption (%)
Soda lime	9.93	0.56	94
noXon	10.18	0.17	98
Zeolite	10.20	0.13	99

Table 2 Transformation of nitrogen dioxide (NO_2/N_2) to nitric oxide (NO) during passage through the three different filter materials

	NO_2/NO without absorber (ppm)	NO after absorber (ppm)	Transformation of NO_2 to NO(%)
Soda lime	9.93/1.30	0.30	−10
noXon	10.18/1.10	2.80	+17
Zeolite	10.20/1.10	0.00	−11

We tested three nitrogen dioxide scavenging materials and showed that they all effectively absorbed nitrogen dioxide from a nitrogen dioxide–nitrogen stock gas. However, the situation changed when we tried to scavenge nitrogen dioxide produced in a mixture of nitric oxide–nitrogen and oxygen. In this case the concentration of nitrogen dioxide immediately after the canister was as high as it would have been without the absorber in place, if the concentration of nitric oxide is taken as that measured after the absorber.

The rate at which nitric oxide is oxidized to nitrogen dioxide in the presence of oxygen has been studied in sealed chambers and follows the equation, $-dNO/dt = k \times [NO]^2 \times [O_2]$.[14 15] However, nitric oxide is a free radical with an unpaired electron. Its reaction with other molecules is a complicated process and does not follow simple biochemical mechanisms.[14 16] We have analysed the velocity of this reaction in a dynamic system for delivering inhaled nitric oxide and found that the reaction appears to take place in two steps following the equation:

$$[NO_2] = k_A \times [NO] + k_B \times [NO]^2 \times [O_2] + k_C \times t \times [NO]^2 \times [O_2].$$

An initial fast reaction is followed by slow formation of nitrogen dioxide and this slow phase follows the kinetics described by the equation established in sealed chambers. Nitrogen dioxide formed by the initial, rapid reaction appears immediately after nitric oxide and oxygen come in contact with each other.[3]

Our study indicated that an initial fast reaction between nitric oxide and oxygen and consequently new formation of nitrogen dioxide also appeared immediately after nitrogen dioxide had been effectively scavenged by a filter. It seems unlikely that nitrogen dioxide could pass the absorber without being scavenged as nitrogen dioxide–nitrogen in the absence of active gases is effectively scavenged. In addition, nitrogen dioxide is almost completely absorbed when mixed with nitric oxide in any proportion in an oxygen-free mixture.[11] Even the addition of two soda lime absorbers close to each other in series in the inspiratory limb did not reduce the concentration of nitrogen dioxide further, indicating that oxidation of nitric oxide takes place in a fast and then a slow reaction.[17] These findings are consistent with the hypothesis that a rapid build-up of nitrogen dioxide occurs in the gas phase, despite earlier findings[14] of only a slow "time-dependent" reaction.

The level to which the concentration of nitrogen dioxide rises after having being scavenged by an absorber depends on the concentration of nitric oxide and oxygen after the absorber. We have shown that the initial formation of nitrogen dioxide is proportional to oxygen concentration and the square of nitric oxide concentration, and is not linearly related to time.[3] The initial oxidation of nitric oxide is very rapid and most probably occurs in the deadspace between the grain particles of the filter material or in the deadspace at the end of the canister, or both. This oxidation of nitric oxide leads to decreased concentration of nitric oxide in the gas mixture. Squire, Kightley and Petros also suspected that the reduction in concentration of nitric oxide with soda lime was caused by oxidation of nitric oxide to nitrogen dioxide in the absorber rather than true absorption.[13] The rate of nitric oxide oxidation in the filter may depend on factors such as density, grain size and deadspace. A very rapid reaction between nitric oxide and oxygen explains why filter materials cause a decrease in nitric oxide concentration, new formation of nitrogen dioxide and return to an almost similar proportion between nitrogen dioxide and the delivered and inhaled nitric oxide levels immediately after the canister. This initial formation of nitrogen dioxide is impossible to eliminate by the use of scavengers.

This explains the findings in the original report by Pickett and colleagues[18] who found that soda lime reduced concentrations of nitrogen dioxide at the expense of similar reductions in inhaled concentrations of nitric oxide.[10] In a subsequent study by Ishibe and colleagues,[11] nitrogen dioxide was completely absorbed by soda lime and it was concluded that soda lime is useful for nitrogen dioxide absorption during nitric oxide inhalation therapy. Ishibe and co-workers stated that Pickett's results from the original study had been corrected in subsequent experiments[18] by using electrochemical fuel cells and vertical instead of horizontal placement of the canister. We believe that the results of all three reports are correct, but because nitrogen dioxide was added to the test gas mixtures in the study by Ishibe and colleagues[11] and in the second study by Pickett and colleagues,[18] the readers are misled to believe that the absorbers are very effective during inhalation of nitric oxide. According to our findings, almost all nitrogen dioxide was probably scavenged by the absorbers but as nitric oxide and oxygen concentrations in the experimental gas mixtures were low, little nitrogen dioxide was formed. With an artificially high concentration of nitrogen dioxide before the absorber, it seemed as if the absorber was very effective. In such a test system the author can freely change the effect of the absorber by varying the concentration of the added nitrogen dioxide and the concentrations of nitric oxide and oxygen in the gas mixture. Similarly, a high gas flow decreases the formation of nitrogen dioxide and also affects the results if nitrogen dioxide is added to the gas mixture. In the original report by Pickett and colleagues,[18] spontaneously formed nitrogen dioxide was scavenged and subsequently re-formed. They concluded correctly that there was no role for a nitrogen dioxide scavenger in their system.

That the effectiveness of a nitrogen dioxide scavenger is dependent on the concentration of nitric oxide in a system with a fixed concentration of nitrogen dioxide was shown by Foubert and colleagues who found that the percentage absorption of nitrogen dioxide decreased with increasing concentration of nitric oxide.[12]

Soda lime fails to absorb nitric oxide if the system is free of oxygen and water.[19] Squire, Kightley and Petros[13] found it difficult to scavenge nitric oxide and discovered that the most effective method was to first oxidize nitric oxide to nitrogen dioxide.[13] Continuous oxidation of nitric oxide with oxygen may explain depletion of nitric oxide when soda lime is used in a circle system.[20] If nitrogen dioxide is added to a gas mixture containing nitric oxide but without oxygen and is passed through a soda lime canister, an equimolecular amount of nitric oxide is depleted,[11] but no new nitrogen dioxide can be detected after the absorber. Foubert and colleagues[12] showed that the concentration of nitric oxide decreases with increasing concentration of nitrogen dioxide. This finding indicates that nitric oxide, in addition to oxidation by oxygen, may be oxidized by a non-volatile product formed by the reaction between nitrogen dioxide and soda lime or a volatile product that is immediately consumed by the reaction, with inactivation of nitric oxide. This nitrogen dioxide-dependent depletion of nitric oxide was not apparent in the noXon material where, on the contrary, nitrogen dioxide seemed to be transformed to nitric oxide.

The noXon material was the only scavenger that reduced nitrogen dioxide to values less than without scavenger. One reason could be that it has the ability to transform nitrogen dioxide to nitric oxide. However, in a gas mixture of nitric oxide, oxygen and the nitrogen dioxide produced by them, the final effect was a decrease in nitric oxide concentration, and therefore noXon cannot be defined as a nitrogen dioxide-selective scavenger as Gilly, Krebs and Nowotny[21] suggested. Their nitric oxide, oxygen and nitrogen dioxide mixtures were also prepared with a nitrogen dioxide concentration greater than would have appeared spontaneously, and accordingly they found that the efficacy of the scavenger improved with higher concentrations of nitrogen dioxide.

Zeolite absorbed nitrogen dioxide most effectively, but it also effectively decreased nitric oxide concentrations. The proportion of nitrogen dioxide to delivered nitric oxide after the canister was similar to the theoretical values we calculated. However, as the concentrations of nitric oxide and nitrogen dioxide decreased to below the set concentrations of nitric oxide, the value as a scavenger, defined as nitrogen dioxide concentrations at comparable concentrations of nitric oxide delivered with and without zeolite, could not be assessed directly. A zeolite consists of uniformly sized compartments in which gas molecules can be trapped if the diameter corresponds to the compartment in the zeolite. The density of the absorbed gas could be higher than the density of gas in the liquid phase. This implies that the pressure of each single gas molecule is very high. Hence, if two nitric oxide molecules and one oxygen molecule fit in one compartment, we have very rapid formation of nitrogen dioxide (or the dimer N_2O_4), and this newly formed nitrogen dioxide is also effectively depleted.

Soda lime was of no use as it increased the concentration of nitrogen dioxide relative to the concentration of nitric oxide, probably as a result of increased oxidation in the deadspace of the canister containing the filter material.

In summary, our tests showed that there is a limited role for nitrogen dioxide scavengers in this delivery system. Zeolite decreased concentrations of nitrogen dioxide and nitric oxide substantially. Of the two other nitrogen dioxide scavengers, noXon was the only one that reduced nitrogen dioxide to concentrations less than those without a filter.

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In vitro degradation of atracurium and cisatracurium at pH 7.4 and 37°C depends on the composition of the incubating solutions

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Summary

The pharmacokinetic models proposed for atracurium or cisatracurium are based on the assumption that spontaneous degradation via Hofmann elimination proceeds *in vivo* at the same rate as measured *in vitro* at pH 7.4 and 37°C. As different degradation rates have been reported for all 10 stereoisomers of atracurium measured together, for each of its three isomeric groups, and for the single isomer cisatracurium, we studied if the rate is dependent on factors other than pH and temperature. *In vitro* degradation of atracurium and cisatracurium was studied at 37°C and pH 7.4 in nine incubating solutions containing one of three buffer systems (phosphate, HEPES or Tris) and additives (sodium chloride, potassium sulphate or glucose). Concentrations of atracurium, cisatracurium and laudanosine were measured after incubation for up to 240 min using an HPLC method. Degradation of atracurium proceeded monoexponentially. The rate was slower in the presence of sodium chloride, potassium sulphate, and in a lower concentration of the phosphate buffer. Glucose enhanced the degradation. At the same total buffer concentration (50 mmol litre^{-1}), degradation was fastest in the phosphate, intermediate in the HEPES and slowest in the Tris buffer. Degradation rates of cisatracurium in sodium phosphate 50 mmol litre^{-1} and Sörensen (Na–K phosphate) buffer 66.7 mmol litre^{-1} were similar to those of atracurium. We conclude that, at constant pH and temperature, the degradation rate of atracurium was dependent on the total concentration of the base in the incubating solution. (*Br. J. Anaesth.* 1998; **81**: 409–414).

Keywords: neuromuscular block, atracurium; neuromuscular block, cisatracurium; pharmacokinetics, atracurium; pharmacokinetics, cisatracurium

Inhibition of neuromuscular transmission by atracurium is caused by the presence of a quaternary nitrogen at each of the two bulky ends that are linked by an aliphatic chain. In chemical terms, atracurium is characterized by two reverse esters in the chain and four chiral centres at each bulky end. The reverse esters facilitate the fission of the chain via an elimination reaction, commonly known as Hofmann elimination. Laudanosine and a quaternary acrylate are the degradation products (fig. 1). The esters may also be hydrolysed by carboxyl esterase yielding a quaternary acid and a quaternary alcohol. As the elimination reaction requires a reversed ester two carbon atoms distant from the quaternary nitrogen and the condition is satisfied in the quaternary acrylate metabolite, this product may undergo a further elimination reaction to yield a second molecule of laudanosine and a bis-acrylate. The quaternary acid does not undergo the elimination reaction.

Because of the presence of four chiral centres, the atracurium molecule is present in 10 steric configurations. The 10 isomers may be arranged in three isomeric groups labelled *cis-cis*, *cis-trans* or *trans-trans*. Recently, the 1R-cis,1'R-cis isomer was isolated and named cisatracurium. The *cis-cis* isomeric group constitutes approximately 57.8%,[1] and cisatracurium approximately 14%,[2] of the atracurium mixture. Degradation of atracurium *in vitro* at pH 7.4 and 37°C was estimated previously for all 10 stereoisomers together,[3] for each of the three isomeric groups separately,[1] and for the single stereoisomer cisatracurium.[2] The reported degradation rates differed. As the degradation rate of atracurium is important for understanding its fate in the human body and plays a key role in pharmacokinetic modelling, we examined systematically the degradation rates of atracurium and cisatracurium *in vitro* for different clearly defined incubation solutions. In each instance, pH and temperature were maintained constant at 7.4 and 37°C, respectively.

Materials and methods

Atracurium besylate and cisatracurium besylate were supplied by Glaxo-Wellcome Pharma, Vienna, Austria. Acetonitrile (Promochem, Wesel, Germany) was HPLC grade. The buffer labelled Tris was composed of Trizma base and Trizma HCl. Tris[hydroxymethyl]-aminomethane (Trizma base), tris[hydroxymethyl]amino-methane hydrochloride (Trizma HCl) and N-[hydroxyethyl]-1-piperazine-N'-[2-ethane-sulphonic acid] (HEPES) were obtained from Sigma, St Louis, MO, USA. All other

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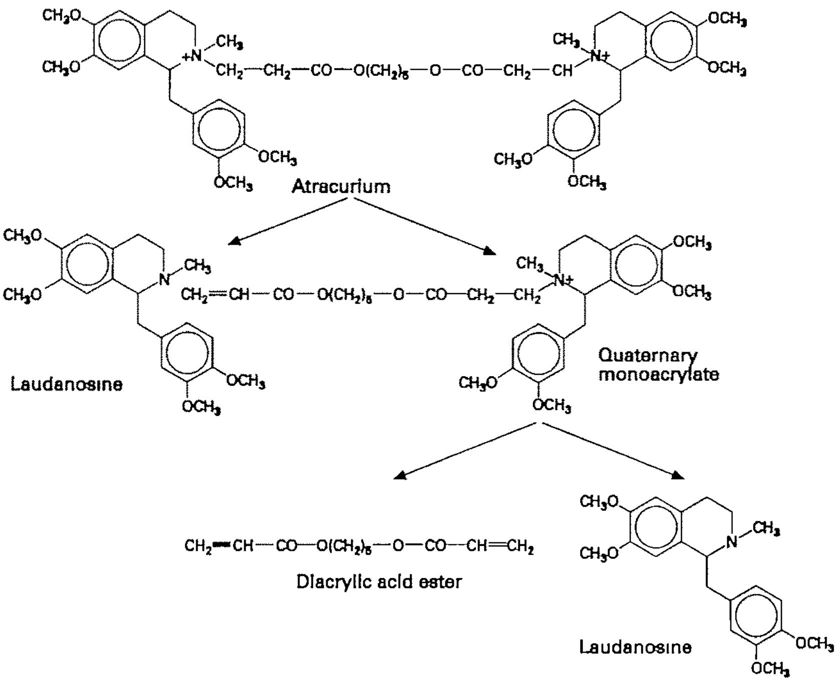

Figure 1 Proposed pathway of atracurium degradation in aqueous buffer solutions.

reagents were obtained from E. Merck (Darmstadt, Germany) and were of analytical grade. Buffers for the calibration of the pH meter were obtained from Radiometer (Copenhagen, Denmark).

The commercially available solution of atracurium (Tracrium 10 mg ml^{-1}) was diluted (1:10) with H_2SO_4 0.005 mol $litre^{-1}$. The diluted solution (25 µl) was added to 10 ml of an incubating solution, mixed well and incubated at 37°C. Similarly, the commercially available solution of cisatracurium (Nimbex, cation concentration 2 mg ml^{-1}) was diluted (1:2) with H_2SO_4 0.005 mol $litre^{-1}$ and 20 µl of the diluted solution added to 10 ml of the incubation solution. At defined times (0, 10, 20, 30, 60, 90, 120, 180 and 240 min) 0.5-ml aliquots were withdrawn, acidified with 10 µl of H_2SO_4 3 mol $litre^{-1}$ and frozen at −20°C until measurement. Concentrations of atracurium, cisatracurium and laudanosine were measured by high pressure liquid chromatography (HPLC). Five to 10 repetitions were carried out for each incubating condition.

A stock solution of phosphate buffer 0.5 mol $litre^{-1}$ was prepared by mixing 82 ml of disodium hydrogen phosphate (Na_2HPO_4) 0.5 mol $litre^{-1}$ and 18 ml of sodium dihydrogen phosphate (NaH_2PO_4) 0.5 mol $litre^{-1}$. Fresh 1:10 dilutions of the stock solution were prepared daily.

Nine incubating solutions were prepared using three buffers (phosphate, HEPES and Tris) and additives (sodium chloride, potassium chloride, potassium sulphate and glucose). In all incubating solutions, pH was adjusted to 7.4 at 37°C with either the acidic or basic component of the buffer pair as necessary. At the end of each incubation, pH was rechecked and the incubation rejected if pH deviated from 7.40 by more than ± 0.03. The compositions of the incubating solutions and their osmolalities are presented in table 1.

Osmolality was determined using a Fiske One-Ten osmometer (Fiske Ass., Norwood, MA, USA) and pH was measured using the Microprocessor pH meter PH 537 (Wissenschaftlich Technische Werkstaetten, Weilheim, Germany). HPLC was performed using the model 126 HPLC pump with an autosampler model 507 (Beckman Instruments, San Ramon, CA, USA). Separation of laudanosine from parent drug was performed on an Ultrasil HPLC column (SCX 10 µ, 4.6x250 mm). The mobile phases were: (A) 60:40 acetonitrile—Na_2SO_4 0.013 mol $litre^{-1}$ in H_2SO_4 0.005 mol $litre^{-1}$ and (B) 60:40 acetonitrile—Na_2SO_4 0.10 mol $litre^{-1}$ in H_2SO_4 0.005 mol $litre^{-1}$. The following concentration gradient was used: 0–4 min, 100% A; 4–6 min, from 100% A to 100% B; 6–10 min, 100% B; 10–12 min, from 100% B to 100% A; 12–14 min, 100% A. Flow rates were 1.5 ml min^{-1} for A and 2.5 ml min^{-1} for B. The fluorometric detector (Shimadzu Corp., Kyoto, Japan) was set to 280 nm for excitation and 320 nm for emission. The limit of detection was 5 ng ml^{-1} (4 nmol $litre^{-1}$) for atracurium or cisatracurium and 2 ng ml^{-1} (5.6 nmol $litre^{-1}$) for laudanosine.

DATA ANALYSIS AND THE MATHEMATICAL MODEL

A kinetic model was formulated (scheme 1) to represent degradation of the parent compounds (atracurium or cisatracurium) via the elimination reaction. The model describes sequential formation of two laudanosine molecules (Ldn_1 and Ldn_2) from one molecule of atracurium or cisatracurium, the first being formed during the degradation of the parent drug (Atr):

$$\mathrm{Atr} \xrightarrow{k_1} \mathrm{Ldn}_1 + \mathrm{QMA}$$
$$\mathrm{QMA} \xrightarrow{k_2} \mathrm{Ldn}_2 + \mathrm{BA}$$
$$\mathrm{Ldn}_{\mathrm{total}} = \mathrm{Ldn}_1 + \mathrm{Ldn}_2 \qquad \text{Scheme 1}$$

Spontaneous ester hydrolysis was not considered. A single rate constant (k_1) defined both the degrada-

Table 1 Composition and osmolality of the incubating solutions. All incubations were carried out at 37 °C and pH 7.4

Incubating solution	Description	Osmolality (mosmol kg^{-1} H_2O)
A	phosphate 50 mmol litre^{-1} (Na_2HPO_4 41 mmol litre^{-1} + NaH_2PO_4 9 mmol litre^{-1})	123
B	phosphate 50 mmol litre^{-1} + NaCl 136 8 mmol litre^{-1} + KCl 2.7 mmol litre^{-1}	373
C	phosphate 50 mmol litre^{-1} + K_2SO_4 100 mmol litre^{-1}	338
D	phosphate 50 mmol litre^{-1} + glucose 300 mmol litre^{-1}	430
E	phosphate 66.7 mmol litre^{-1} — Sörensen (Na_2HPO_4 66.7 mmol litre^{-1} + KH_2PO_4 66.7 mmol litre^{-1})	155
F	phosphate 8 mmol litre^{-1} (Na_2HPO_4 6.5 mmol litre^{-1} + KH_2PO_4 1 5 mmol litre^{-1}) + NaCl 136.8 mmol litre^{-1} + KCl 2.7 mmol litre^{-1}	286
G	HEPES buffer 50 mmol litre^{-1}	74
H	Tris buffer 50 mmol litre^{-1} (Trizma-HCl 36.3 mmol litre^{-1} +Trizma-base 13.7 mmol litre^{-1})	93
I	Tris buffer 200 mmol litre^{-1} (Trizma-HCl 145.2 mmol litre^{-1} +Trizma-base 54.8 mmol litre^{-1})	354

Table 2 The rate constant (mean (SD)) for the degradation of atracurium or cisatracurium and the formation of the first molecule of laudanosine (k_1). The rate constant for the formation of the second molecule of laudanosine is k_2. The half-lives for each rate constant are denoted as $T_{1/2}$

Incubating solution	n	k_1 (min^{-1})	$T_{1/2}$ (min)	k_2 (min^{-1})	$T_{1/2}$ (min)	Coeff of determination range
Atracurium						
A	8	0 0354 (0.0045)	19.6	0.0159 (0.0077)	43.6	0.9610 to 0.9976
B	10	0 0145 (0.0013)	47.9	0.0026 (0.0010)	267	0.9562 to 0.9965
C	5	0.0234 (0.0009)	29.6	0.0182 (0.0078)	37.9	0.9701 to 0.9919
D	10	0.0621 (0.0047)	11.2	0.0179 (0.0085)	38.7	0 9822 to 0.9948
E	5	0.0323 (0.0036)	21.5	0.0183 (0.0030)	37.9	0.9572 to 0.9879
F	10	0.0111 (0.0009)	62.4	0.0140 (0.0085)	49.5	0.9499 to 0.9943
G	10	0.0181 (0.0001)	38.3	0.0028 (0.0002)	248	0.9724 to 0.9975
H	10	0.0099 (0.0005)	70.1	0.0044 (0.0029)	157	0.9921 to 0.9985
I	10	0.0167 (0.0006)	41.5	0.0123 (0.0040)	30.1	0.9940 to 0.9981
Cisatracurium						
A	5	0 0320 (0.0015)	21.7	0 0138 (0.0010)	50.2	0.9873 to 0.9922
E	5	0.0280 (0.0017)	24.8	0.0139 (0.0012)	49.9	0.9461 to 0.9789

tion rate of atracurium and rate of formation of the first molecule of laudanosine (Ldn_1). Quaternary monoacrylate (QMA), formed concurrently with the first molecule of laudanosine, was postulated to undergo further elimination yielding the second molecule of laudanosine and bis-acrylate (BA). The corresponding rate constant was designated k_2. The model was fitted to time-dependent, measured concentrations of atracurium or cisatracurium and to the sum of both laudanosine molecules (Ldn_{total}) in each experiment; the respective half-lives were calculated as $T_{1/2}=\ln(2)/k$. Equations describing these processes are presented in the appendix. The mean values for the rate constants for each incubating solution were calculated with the corresponding standard deviations; the goodness of fit was defined by the coefficient of determination. The coefficients of determination are presented as the range of the worst and best fits.

Results

Results obtained by incubating atracurium or cisatracurium at pH 7.4 and 37°C are presented in table 2.

The initial concentration of atracurium in the incubating solutions was 1.75 (SD 0.43) µmol litre^{-1}, that of cisatracurium 1.61 (0.23) µmol litre^{-1} and that of laudanosine 0.055 (0.037) µmol litre^{-1}. Degradation of atracurium proceeded monoexponentially in all incubating solutions. The rate constant k_1 varied markedly between the incubating solutions (incubating solutions A to I, table 2). Accordingly, the formation rates of laudanosine varied; under all incubating conditions the total concentrations of laudanosine at the end of the incubations were compatible with the postulate that one molecule of atracurium degrades into two molecules of laudanosine. With the exception of the incubating solutions F and I, the formation of the second molecule of laudanosine proceeded at a slower rate than the formation of the first molecule (table 2). For each incubating solution, the coefficients of determination for the best and worst fits are also presented in table 2. The ranges demonstrate that the proposed model for the degradation of atracurium or cisatracurium and the formation of laudanosine fitted the data well under all experimental conditions.

Two experiments representing fast (phosphate buffer 50 mmol litre^{-1}, incubating solution A) and slow degradation of atracurium (Tris buffer 50 mmol litre^{-1}, incubating solution H) are illustrated in figure 2. The two experiments were selected as representative as their coefficients of determination were the medians in the respective groups.

The influence of ions and glucose on the degradation of atracurium became evident by pair-wise comparison of the rate constants k_1 in phosphate buffer 50 mmol litre^{-1} (incubating solutions A, B, C and D) (table 2). Addition of sodium chloride 136.8 mmol litre^{-1} and potassium chloride 2.7 mmol litre^{-1} decreased the rate of atracurium degradation (group A *vs* group B). Similarly, potassium sulphate 100 mmol litre^{-1} also decreased the degradation rate compared with the rate in plain phosphate buffer but the effect

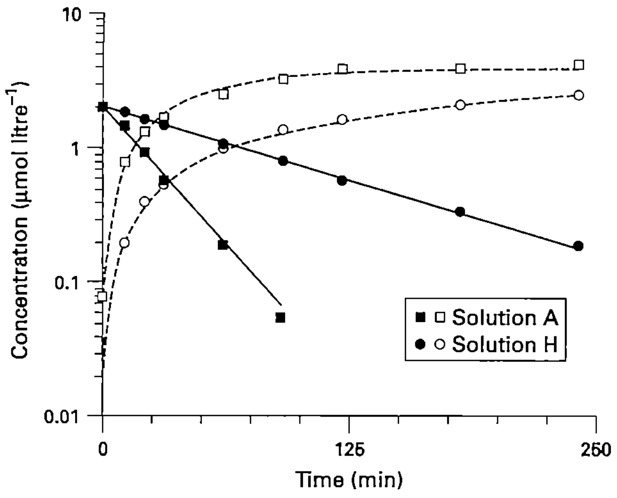

Figure 2 Degradation of atracurium (filled symbols) in phosphate buffer 50 mmol litre^{-1} (solution A) and Tris buffer 50 mmol litre^{-1} (solution H). Measured total concentrations of laudanosine (open symbols) are shown for solution A and solution H. The continuous and dotted lines were calculated from the model for atracurium decay and the formation of laudanosine, respectively. A monoexponential function fitted both data sets well. The faster degradation of atracurium resulted in a faster formation of laudanosine and the amount of laudanosine formed within 240 min of incubation corresponded to twice the initial amount of atracurium. The slower degradation of atracurium in the Tris buffer resulted in a slower formation of laudanosine. The amount of laudanosine formed during 240 min of incubation was approximately equal to the added amount of atracurium.

was less pronounced (group A *vs* group C). In contrast, addition of glucose 300 mmol litre^{-1} increased the rate of degradation (group A *vs* group D). The osmolalities of the incubating solutions were increased by the additions to approximately 3–3.5 times that of the plain phosphate buffer (table 1).

A difference in the degradation rates between the low (8 mmol litre^{-1}) and high (50 mmol litre^{-1}) phosphate concentration solutions is evident from the comparison of group B and group F (table 2). Sodium chloride and potassium chloride were present in both buffers as in the experiments described previously, but the total concentration of potassium in solution B was approximately 2.7 mmol litre^{-1}, whereas in solution F it was approximately 4.2 mmol litre^{-1}. Degradation of atracurium proceeded at a slower rate in the lower phosphate concentration solution. A slightly higher phosphate concentration in conjunction with a high concentration of potassium (66.7 mmol litre^{-1}, group E) did not alter the degradation half-life of atracurium (group A *vs* group E). Degradation proceeded markedly faster when the concentration of the Tris buffer was increased from 50 to 200 mmol litre^{-1} (group H *vs* group I).

Incubation of atracurium in three different buffers, each at 50 mmol litre^{-1}, demonstrated considerably different degradation rates (group A *vs* group G *vs* group H) (table 2). The rate was fastest in the phosphate buffer (group A) and slowest in the Tris buffer (group H). The rate in HEPES buffer (group G) was intermediate.

Degradation of cisatracurium was measured in the incubating solutions A and E (table 2). The rates of degradation were comparable under these conditions. Moreover, the estimated rates for the degradation of cisatracurium were similar to those for atracurium incubated under identical conditions.

Discussion

The results of incubations in different solutions, but under constant pH (7.4) and temperature (37°C), demonstrated markedly different rates of degradation of atracurium. In comparison with degradation in plain sodium phosphate buffer 50 mmol litre^{-1}, addition of sodium chloride or potassium sulphate markedly retarded the degradation while the addition of glucose increased the rate. The rates were also different in three buffers, at concentrations of 50 mmol litre^{-1}. In phosphate buffers, solutions A and E, degradation of cisatracurium was comparable with that of atracurium. Under all incubating conditions the rates of degradation of atracurium or cisatracurium showed monoexponential decay and formation of two molecules of laudanosine from one molecule of atracurium or cisatracurium.

Would separate measurements of each of the 10 isomers yield results different from those we obtained by measuring all as atracurium? We are convinced that such an analytical approach would not have altered the results. First, the degradation rates of atracurium and of the single stereoisomer cisatracurium demonstrated no systematic differences. Second, the results by Tsui, Graham and Torda[1] also support the notion that the three isomeric groups of atracurium decay at the same rate. Given the composition of 57.8% *cis-cis*, 36.5% *cis-trans* and 5.7% of the *trans-trans* isomeric groups, the authors reported corresponding degradation half-lives of 57.1, 59.7 and 66.4 min; hence decay of the *trans-trans* isomeric group was significantly slower.[1] Thus separate measurement of the individual stereoisomers would probably not have yielded results different from those we observed in their mixture.

Our estimates of the rates of degradation of atracurium or cisatracurium confirm the apparently diverging results reported previously. In Tris buffer 50 mmol litre^{-1}, Merrett, Thompson and Webb[3] reported a half-life for atracurium of approximately 70 min; in this buffer we obtained identical results for atracurium ($T_{\frac{1}{2}}$=70.1 min, incubating solution H). For the *cis-cis* and *cis-trans* isomeric groups of atracurium (representing approximately 94% of atracurium) Tsui, Graham and Torda[1] reported half-lives in "buffered saline" of approximately 57 and 60 min, respectively. In our experiments the half-life for the atracurium mixture in the same buffer (incubating solution F) was 62.4 min. Stiller, Cook and Chakravorti[4] found a half-life of atracurium of 58 min in Sørensen buffer at pH=7.3, whereas in our experiments in Sørensen buffer (incubating solution E) the degradation half-life of atracurium was 22 min and that of cisatracurium 25 min. As the exact composition of the buffer used by Stiller, Cook and Chakravorti[4] was not reported, the longer half-life observed in their studies may be explained by differences in the buffer composition and a lower pH value.

Welch and colleagues[2] reported a half-life for cisatracurium of 34 min in sodium phosphate buffer 67 mmol litre^{-1} supplemented with sodium chloride

77 mmol $litre^{-1}$ and bovine serum albumin 1.5 g dl^{-1}. Although our incubating solution E differed from that used by Welch and colleagues,[1] addition of sodium chloride might have retarded the degradation of cisatracurium as we demonstrated for atracurium in sodium phosphate buffer 50 mmol $litre^{-1}$ (solutions A and B). However, a potential influence of albumin remains unclear.

The finding that sodium and potassium ions or glucose influence the elimination reaction of atracurium was surprising, and we cannot offer a satisfactory explanation. An increase in osmolality *per se* should result in an opposite effect (comparable with the addition of glucose, incubation solution D).

The proposed model for the degradation of atracurium and the generation of laudanosine adequately explained the results under all incubating conditions. The first rate constant characterizing the degradation of atracurium or cisatracurium (k_1) was calculated from the degradation rates of the parent drug. We consider the rate constant k_1 a reliable estimate for the generation of the first molecule of laudanosine. As the measured concentrations of laudanosine represented the total concentrations of laudanosine, generation of the second laudanosine molecule was derived as the difference between the measured concentration and estimated concentration of the first laudanosine molecule. Estimate of the second rate constant, k_2, must be considered an approximation. Therefore, comparison of the two rate constants is not justified and no statement can be made as to whether or not the two molecules of laudanosine are formed at similar or different rates. We see the importance of reporting the rate constant k_2 not in its absolute value but in confirming the working hypothesis that the decay of atracurium and cisatracurium conforms with the proposed degradation pathway (fig. 1) with each molecule of the parent compound producing two molecules of laudanosine. In turn, confirmation of this pathway implies that hydrolysis of the parent compounds probably did not occur during the incubations.

The most striking results of our study was the different degradation rate of atracurium in three buffers of identical pH and concentration (pH 7.4, 50 mmol $litre^{-1}$, incubating solutions A, G and H). The results either argue for an influence of the nature of the buffer base itself on the elimination reaction or of the different concentrations of base in the buffer. As Hofmann elimination is a base-catalysed reaction,[5] it depends on the concentration of all of the bases. By definition, pH provides information only on the concentration (activity) of the hydroxide anion but not on the concentration of other bases.

In a buffered solution the concentration of the base is determined by the equilibrium dissociation constant of the buffer pair (p*K*), concentration (activity) of the hydrogen ions (pH), temperature and total buffer concentration. The theoretically derived curve for different buffers in concentrations of 50 mmol $litre^{-1}$ at pH 7.4 is represented by the continuous line in the upper panel of figure 3. The concentration of the base in each of three buffers used in our experiments is indicated (p*K* values are those for 25°C). It is evident that the concentration of the base decreases with higher p*K* values. Using these data, we plotted the degradation half-lives of atracurium against the estimated concentration of the base for each buffer (lower panel in fig. 3). Clearly, degradation of atracurium is enhanced by the increase in base concentration. The conclusion is strengthened further by our observation that degradation is faster in the solutions of a higher total concentration of the Tris (incubation solution H and I) and the sodium phosphate (incubation solution F and B) buffers. The influence of different total concentrations of the same buffer is, however, not as pronounced as that of different buffer bases at identical concentrations.

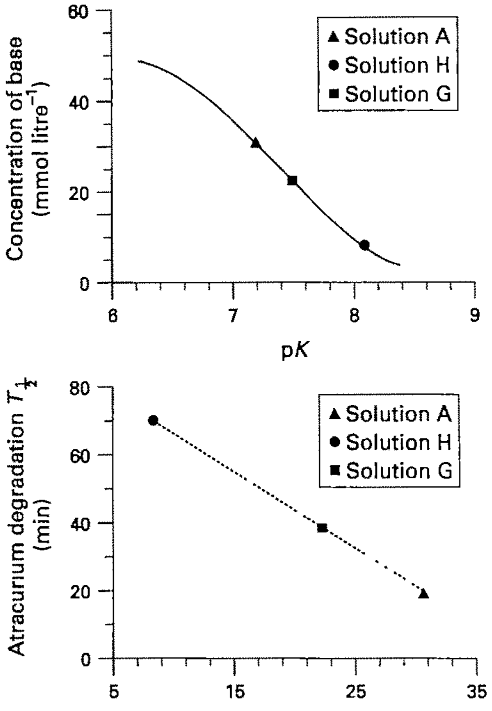

Figure 3 Top: the continuous line represents the concentrations of the base in 50 mmol $litre^{-1}$ of buffer solutions as related to the equilibrium dissociation constant of the buffer pair (p*K*). Concentrations were based on the equation of Henderson–Hasselbach and the p*K* values at 25°C.[8,9] The symbols indicate the buffer pair: phosphate (solution A, second step); Tris buffer (solution H); and HEPES buffer (solution G). Bottom: relationship between the degradation half-lives for atracurium and the concentration of bases in the three buffers presented in the upper panel. The dotted line connects the points.

Some investigators[1-4] reported faster decay of atracurium in plasma than in a solution buffered to pH 7.4. The observation was explained by postulating ester hydrolysis as an additional degradation pathway. In view of our results, the interpretation needs to be re-evaluated as the rate of degradation in the buffered solution depends on the type and concentration of the buffer. As documented in table 2, the rate of degradation may be much faster or appreciably slower than that in plasma ($T_{\frac{1}{2}}$ approximately 22 min).

Understanding Hofmann elimination of atracurium or cisatracurium as a base-catalysed reaction implies that the degradation rates measured *in vitro* may not be representative of the rates *in vivo*. No incubation solution, including plasma, may correctly represent the actual situation *in vivo*, as (i) plasma contains a variety of different bases in unknown concentrations, (ii) in circulating blood, drugs come into contact with red blood cells and the intima of the blood vessels with unknown concentrations of bases and ions, and (iii) the distribution of atracurium or cisatracurium in the extracellular space exposes the drugs to the bases lining the outer surface of cells. We suggest that the assumption common to all pharmacokinetic models of atracurium,[6 10] or cisatracurium,[7] namely that degradation proceeds at the same rate everywhere in the body and is equal to that measured *in vitro*, needs to be re-evaluated.

Appendix

Time-dependent molar concentrations are represented by square brackets. The model for cisatracurium is similar to that of atracurium when the symbols for atracurium are replaced by those for cisatracurium. The apparently monoexponential decay of atracurium may be represented by:

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{Atr}] = -k_1 \times [\mathrm{Atr}] \tag{1}$$

The estimate for [Atr] at t=0 min was the concentration of atracurium measured at this time.

The first molecule of laudanosine is generated at the rate estimated for atracurium degradation and the rate constant is identical to that for the degradation of atracurium.

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{Ldn}_1] = k_1 \times [\mathrm{Atr}] \tag{2}$$

The estimate for $[\mathrm{Ldn}_1]$ at time 0 min was the concentration of laudanosine measured at this time. The estimate was treated as a constant and was not allowed to float.

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{QMA}] = k_1 \times [\mathrm{Atr}] - k_2 \times [\mathrm{QMA}] \tag{3}$$

Quaternary monoacrylate (QMA) is formed at the same rate as the first molecule of laudanosine and it decays further with the rate constant k_2. The initial concentration of QMA was assumed to be zero.

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{Ldn}_2] = k_2 \times [\mathrm{QMA}] \tag{4}$$

The second molecule of laudanosine ($[\mathrm{Ldn}_2]$) is formed from QMA with the rate constant k_2. The initial concentration of $[\mathrm{Ldn}_2]$ was set to zero.

$$[\mathrm{Ldn}_{\mathrm{total}}] = [\mathrm{Ldn}_1] + [\mathrm{Ldn}_2] \tag{5}$$

The measured concentration of laudanosine corresponds to the total concentration of laudanosine ($[\mathrm{Ldn}_{\mathrm{total}}]$).

The best estimates for the rate constants k_1 and k_2 were obtained by solving simultaneously equations (1)–(5) using the program Scientist (MicroMath, Salt Lake City, UT, USA). The coefficient of determination as a measure of goodness of fit was also provided by this program. Each experiment was evaluated separately and the calculated rate constants were averaged for each incubating solution.

Acknowledgments

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I.v. anaesthesia and EEG burst suppression in rats: bolus injections and closed-loop infusions

P. C. M. Vijn and J. R. Sneyd

Summary

We describe a system for monitoring and controlling i.v. anaesthesia in rats using burst suppression ratio (BSR) detection in the extradural EEG. After bolus injection, peak BSR values of 95% were achieved with propofol 8 mg kg^{-1}, etomidate 3.5 mg kg^{-1} and alphaxalone 4.5 mg kg^{-1}. Thiopental 32 mg kg^{-1} produced a peak BSR of 70% (larger doses were not tolerated). Recovery was fastest with propofol, followed by etomidate and alphaxalone with equal duration, and slowest with thiopental. In further experiments, a closed-loop infusion system maintained BSR accurately at targets of 30%, 50%, 70% or 90% for 60 min with propofol or etomidate. During these experiments the infusion rates were found to decrease with time, more so with etomidate (approximately 40%) than with propofol (approximately 20%). Recovery times were 2–3 times longer with etomidate than with propofol. This model demonstrated differences between i.v. anaesthetics and may be useful in screening new compounds in preclinical development. (*Br. J. Anaesth.* 1998; **81**: 415–421).

Keywords: rat, monitoring, electroencephalography; anaesthetics i.v., propofol; anaesthetics i.v., etomidate; anaesthetics i.v., thiopental; anaesthetics i.v., alphaxalone

Improved understanding of the pharmacokinetics and pharmacodynamics of i.v. anaesthetics during the past decade has facilitated their widespread use. These advances are illustrated in the clinical use of target-controlled infusion (TCI) systems based on population variables[1] but also in articles addressing clinical predictors such as context-sensitive half-time, relevant effect-site decrement time and mean effect time.[2-4] Development of new i.v. anaesthetics should build on knowledge of current drugs and determine key characteristics at an early stage. One such characteristic is the tendency to accumulation with prolonged infusion and consequent delay in recovery.

Glen anaesthetized mice with propofol[5] and, when they recovered, administered the same dose again and repeated this process through multiple cycles. Recovery times after these repeated injections were similar. In contrast, with thiopental, accumulation led to rapidly increasing recovery times. Thus simple experiments with small animals may provide useful discrimination between i.v. anaesthetics. However, such repeated dose experiments do not achieve steady state nor do they indicate if stable anaesthesia can be maintained.

In closed-loop systems for drug delivery, the effect of a drug is measured and used to adapt the rate of infusion to approach target-effect values. Closed-loop systems have been described in animals,[6] in patients[7 8] and in simulation[9] studies. In principle the feedback in these systems may account for sources of variability in the processes between drug delivery and drug response, of which the most obvious is the inaccuracy of population pharmacokinetic models as applied to individuals in open loop TCI systems. For use during early phases of drug discovery, a pharmacokinetic model is not yet available. In this investigation we evaluated the use of a closed-loop system with i.v. anaesthetics in the absence of a pharmacokinetic model to determine if such a system might, in the future, provide useful new information on new drugs.

For this purpose, an adaptive, integrative and proportional feedback module is described to maintain a constant EEG effect during 60-min infusion periods with propofol and etomidate.

Before designing a closed-loop system, a reliable measure of drug effect is required. Intermittent cortical activity known as burst suppression (BS) in the human electroencephalogram (EEG) has been noted since 1936, occurring after large doses of barbiturates and some volatile anaesthetics.[10] Quantitative animal data on BS are sparse, with the exception of threshold methods, where drugs are titrated to induce BS periods of 0.5 s or longer.[11 12] BS patterns induced by isoflurane and enflurane in the pig,[13] and by propofol and isoflurane in rabbits[14] have been studied, and differences in BS states induced by different hypnotics in rats have been emphasized.[15] Thus BS appears to be a general phenomenon occurring with many different classes of anaesthetic drugs. Rampil and Laster[16] introduced computerized BS extraction with isoflurane in the rat, where a time continuous BS measure on a graded scale expressed the percentage of time where the EEG was quiescent. We have adapted and optimized this technique to i.v. anaesthetics in the rat and used the EEG variable for feedback in a closed-loop system.

Materials and methods

Studies were performed at Organon Laboratories in the Netherlands in accordance with Dutch animal welfare regulations. Male Wistar rats, weighing 220–300 g, were maintained in a 12-h light–dark

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cycle (lights on at 13:00), housed individually, and allowed free access to food and water. Experiments were performed between 09:00 and 13:00. For this study, 41 animals were used: 17 received bolus injections, 24 received closed-loop infusions. Some animals in the bolus group were used repetitively, with a minimum of 1 week between injections.

EEG ELECTRODES: SURGICAL PROCEDURE

Rats were instrumented with chronically implanted extradural electrodes. Briefly, rats weighing approximately 200 g were anaesthetized with pentobarbital 60 mg kg^{-1} i.p. and placed in a stereotactic frame. The skull was exposed and four small stainless steel electrodes (diameter 0.6 mm) were positioned through the skull with their tips just touching the dura mater at stereotactic co-ordinates: (electrode 1) A (anterior) 6 (mm) L (lateral) 3 (mm), (electrode 2) A6L-3, (electrode 3) A0L0 and (electrode 4) A10L2 relative to the lambda. The electrodes were wired to a small connector, fixed with dental cement and the skin was closed, leaving access only to the upper part of the connector. Buprenorphine 0.05 mg kg^{-1} s.c. was administered for postoperative analgesia and the rats were returned to their cages for at least 1 week before the start of an experiment.

EEG RECORDING

A shielded cable led from the connector on the rat's head to custom-built amplifiers. Two symmetrical potential differences were recorded, between electrodes 1 and 3, and between electrodes 2 and 3, respectively. Electrode 4 was used as the ground electrode. EEG was amplified 5100 times, filtered (–3 dB@0.16 Hz; 6 dB oct^{-1} to –3 dB@200 Hz; 12 dB oct^{-1}) and digitized at 641.03 Hz with 12-bit resolution (1:4096, corresponding to 0.479:1961 µV) by a signal processor (Cambridge Electronic Design, model 1401, Cambridge, UK) interfaced to a PC running MS-DOS.

BOLUS INJECTION

Injections were made with a computer-controlled laboratory infusion pump (Harvard Apparatus, model 44, Edenbridge, UK) into a tail vein, with 25-gauge needles connected with 250 mm of Teflon tubing (inner diameter 0.56 mm) to 1-ml syringes. Duration of drug injection was 10 s and injection volume was 0.2–0.4 ml. Rats were restrained gently by hand between needle insertion and loss of righting (typically 30 s). EEG recording commenced at the start of the bolus injection, after having verified that baseline EEG was normal and artefact-free by visual inspection on the PC screen.

CONTINUOUS INFUSION

One to two hours before the experiments the rat was instrumented with a tail vein catheter (Braunule, Braun, 22G). For infusion, this catheter was connected with 250 mm of Teflon tubing (inner diameter 0.56 mm) to 2.5-ml syringes. Infusion pump, restraining of animals and start of EEG recording were identical to the bolus injection protocol.

DRUGS

Standard commercial preparations of propofol (Diprivan 10 mg ml^{-1}, Zeneca), etomidate (Hypnomidate 2 mg ml^{-1}, Janssen) and thiopental (Nesdonal 25 mg ml^{-1}, Rhône Mérieux) were tested. Crystalline alphaxalone (Organon) was dissolved in 10% hydroxypropyl-ß-cyclodextrin (Aldrich) at a concentration of 5 mg ml^{-1}.

MONITORING ANAESTHESIA, BSR EXTRACTION

The digitized EEG was processed online to extract a time-continuous measure for the percentage of BS (BS ratio, BSR). BSR is the percentage of time per 15-s epoch spent in suppression where suppression is defined as an interval where the amplitude of the time-differentiated EEG signal stays within a –15 to 15 µV window for at least 100 ms. The principal difference from Rampil and Laster's definition[16] is temporal differentiation. This step enhances higher frequency components while attenuating lower frequency components in the EEG signal, eliminating slow baseline drifts and delta activity while amplifying transient bursting activity. This greatly enhances the sensitivity of BSR extraction. Time differentiation was performed digitally by taking the differences between each two successive samples in the digitized EEG. The definition of BSR sets the upper limit of BS detection (BSR=100%) equal to a 15-s period without bursts, which only occurs after high doses of general anaesthetics.

Maximum sensitivity of BS detection was guaranteed by the following procedure: from 5 min of baseline EEG of six untreated rats (30 min of EEG in total), recorded during pilot experiments preceding the experiments for this study, a search algorithm repeatedly determined BSR, starting with 100 µV for the voltage threshold and 100 ms for the minimum allowed BS duration. The threshold value was decreased gradually until no single epoch of BS was detected in this baseline EEG, which occurred at 15 µV. BSR extraction with the selected variable values was tested extensively in pilot experiments and found to compare well with visual detection of BS epochs. The intermediate steps in BSR extraction are illustrated in figure 1.

Both recorded EEG channels were processed, resulting in two BSR values. Results and rats were discarded if large systematic differences (>15%) indicated asymmetry in the electrode implantation. Any BSR reported in this article is the average of two single channel BSR values. The algorithm is implemented in Pascal (Microsoft) and combined with EEG monitoring routines, infusion pump drivers and a user interface into integrated programs running on a PC.

CLOSED-LOOP SYSTEM

Induction of anaesthesia

At the start of an experiment, anaesthesia was induced with a loading dose injected at a rate of *Iind* for 30 s. *Iind* was chosen to deliver in 30 s the dose which was predicted to produce the appropriate BSR in the bolus experiments. The infusion rate was then reduced to 0.2×*Iind* until 60 s when the closed-loop

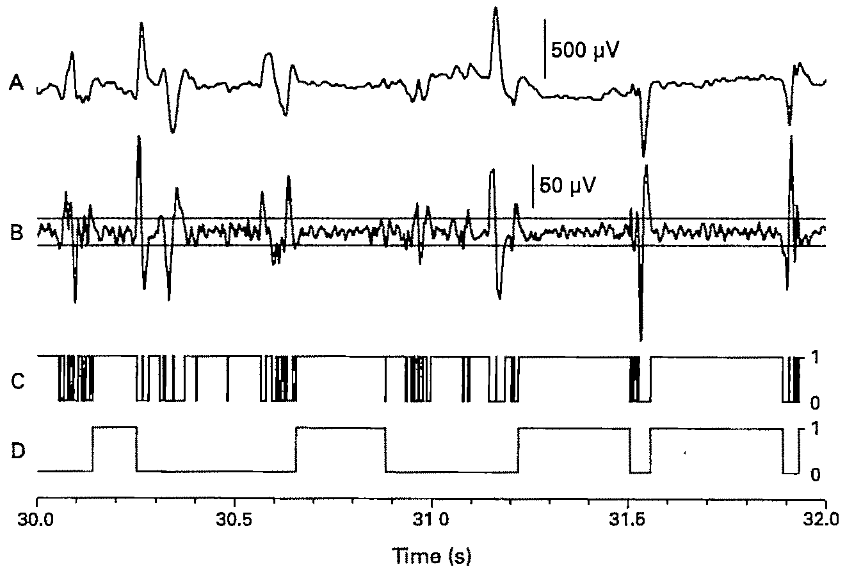

Figure 1 Illustration of the method used to determine burst suppression ratio (BSR) A: 2 s of EEG, as recorded 30 s after i.v. injection of propofol 8 mg kg^{-1} over 10 s. B: Two-point digitally differentiated version of A. The horizontal lines are the borders of the amplitude window for BS detection. C: Binary signal, with the value 0 if trace B is outside the amplitude window, and 1 if it is within the window. D: BS signal, where "within window" periods shorter than 100 ms in C are cancelled. From 15 s of this signal BSR is calculated, which approximates 50% in this example.

system took over. Rats were restrained gently by hand until loss of righting. Although the specific value for *Iind* determined the speed of induction of anaesthesia and the initial accuracy of approaching the BSR target, an inappropriate value would readily be corrected by the closed-loop system.

Maintenance of anaesthesia

The feedback algorithm was in effect from 1–60 min after the start of drug infusion. Briefly, the discrete, constant flow of BSR (one value per second) was presented at the input of a signal processing algorithm. The output of this algorithm controlled the infusion pump. The algorithm essentially increased the infusion rate if the actual BSR was smaller than the pre-set BS target and vice versa, while at the same time it adapted the set-point of this proportional system according to a rough estimate of the time characteristics of the drug being tested. The system is fully characterized by two equations, the first describing adaptation of the system on a relatively long time scale of several minutes, the second describing the instantaneous corrections (each second) of drug infusion.

Moving average filter

At each time step *j*, equal to 1 s, a weighted average of the infusion rate signal *I* during the past *N* seconds is calculated as:

$$M_j = \sum_{i=0}^{N-1} D_i I_{j-i} \qquad (1)$$

M is thus the convolution of *I* and *D*. *D*=drug-specific part of the feedback model and can optimally be derived from an accurate pharmacokinetic–pharmacodynamic analysis for the individual being tested. As we wished to develop this system in a drug development setting, such a model is assumed not to be known for these experiments and a population mean estimate is used instead: the function *D* is filled with the averaged BSR response measured after bolus injection in a group of animals, and normalized such that the sum of all *N* non-zero coefficients of *D* (the area under the curve of the function *D*) is equal to 1 to convert it to a weighting function.

M determines the set-point of the feedback system at each instant of time: it represents the anticipated infusion rate that, given the recent history of infusion rates and the known time response of the drug, maintains BSR at its target value. If, at the start of an experiment, I_{j-i} refers to an infusion rate before the closed-loop mode is in effect (*j-i<60*), the initially selected maintenance rate at 0.2×*Iind* is used instead.

Determining new infusion rate

For optimal performance, corrections to deviations from the BSR target need to be made as early as possible. To achieve this, at each time step a new actual infusion rate value is calculated from the current BSR (B_j) and the anticipated infusion rate set-point (M_j) as:

$$I_j = M_j\left(1 + \frac{S(T - B_j)}{T}\right) \qquad (2)$$

where *S* controls the amplification of the feedback loop and *T* is the BSR target.

Stimulus–response measurement

To obtain an indication of the degree of reflex suppression during steady state anaesthesia, a mild pressure stimulus (140 g mm^{-2}, 8 mm^2, 0.5 s) was applied to one of the hind toes of the rat at the 50th minute of the continuous infusion. The paw withdrawal response was scored qualitatively as none, weak, moderate or normal.

Results

BOLUS INJECTIONS

The four drugs were tested at multiple doses (on average four) on four animals per dose. BS patterns induced by the four drugs were consistent and reproducible. With all drugs tested, BS started to develop at a dose only slightly higher than needed to induce loss of righting reflex. The maximum BSR and persistence of BS increased with increasing dose. Figure 2 shows BSR curves from individual rats treated with propofol 8 mg kg^{-1}, etomidate 3.5 mg kg^{-1}, thiopental 32 mg kg^{-1} and alphaxalone 4.5 mg kg^{-1}, respectively. These doses were found to be the lowest to produce a peak BSR larger than 90% in all four rats per group, except for thiopental, where doses larger than 32 mg kg^{-1} resulted in excessively long recovery times and respiratory depression. The four drugs yielded different shaped BSR curves. Propofol and thiopental showed a faster initial decay in BSR than alphaxalone and etomidate. BSR persisted longer after thiopental compared with the other agents. With propofol, BSR returned fastest to baseline. The times to regain righting reflex, as indicated by the arrows, corresponded with BSR approaching zero.

CONTINUOUS INFUSIONS

The drug-specific moving average functions D in equation (1) for propofol and etomidate are shown in figure 3. These were obtained by averaging the measured BSR responses to the bolus injections of propofol 8.0 mg kg^{-1} and etomidate 3.5 mg kg^{-1} (n=4/drug), smoothing the resulting curves and normalizing the area under the curve to a value of 1.

In pilot experiments we found that values for S in the range 3–7 performed well and S was fixed at a value of 5. During the first 10 min after the start of an experiment, there were marked fluctuations in BSR and infusion rate. During this phase the system was adapting to the response to the initial bolus infusion, which often had an undershoot or overshoot depending on the drug sensitivity of the animal being tested. As an example, figure 4 shows the first 5 min of a propofol closed-loop infusion experiment, where the BSR target T was 70% and the induction rate *Iind* was 18 mg kg^{-1} min^{-1} (corresponding to an induction dose of 9 mg kg^{-1} over 30 s). After the initial predetermined infusions during the first minute, the BSR target was not reached, and the system responded immediately by increasing the infusion rate to correct this. When the BSR target was reached, a slight overshoot occurred at approximately 2 min. During this overshoot the closed-loop system started to force BSR back to its target by reducing the infusion rate. At 5 min BSR was only slightly above its target.

Typically, within 10 min BSR stabilized around its target. Closed-loop infusion experiments with propofol and etomidate at BSR targets of 30%, 50%, 70% and 90% are shown in figure 5. Each curve represents the mean of three animals. The induction rates for 30%, 50%, 70% and 90% BSR targets were 14, 16, 18 and 22 mg kg^{-1} min^{-1} for propofol, and 5, 6, 7 and 9 mg kg^{-1} min^{-1} for etomidate.

The closed-loop system stabilized BSR at all targets, as can be seen from the BSR traces in figure 5. Performance was also assessed quantitatively in each individual experiment. For this purpose the standard deviation (SD) of the BSR distribution around the BSR target during the 10–50-min time interval (2400 s) was determined according to equation (3). The first 10 min were excluded because of the initial fluctuations, and the last 10 min because in some experiments the paw pressure stimulus influenced BSR stability.

$$\mathrm{SD}=\sqrt{\frac{1}{2400}\sum_{i=600}^{2999}(\mathrm{Bi}-\mathrm{T})^2} \qquad (3)$$

SD never exceeded 5% in any experiment. SD values in the etomidate experiments were not systematically different from SD values in the propofol experiments.

For etomidate, mean infusion rates during the 10–60-min interval to maintain 30%, 50%, 70% or

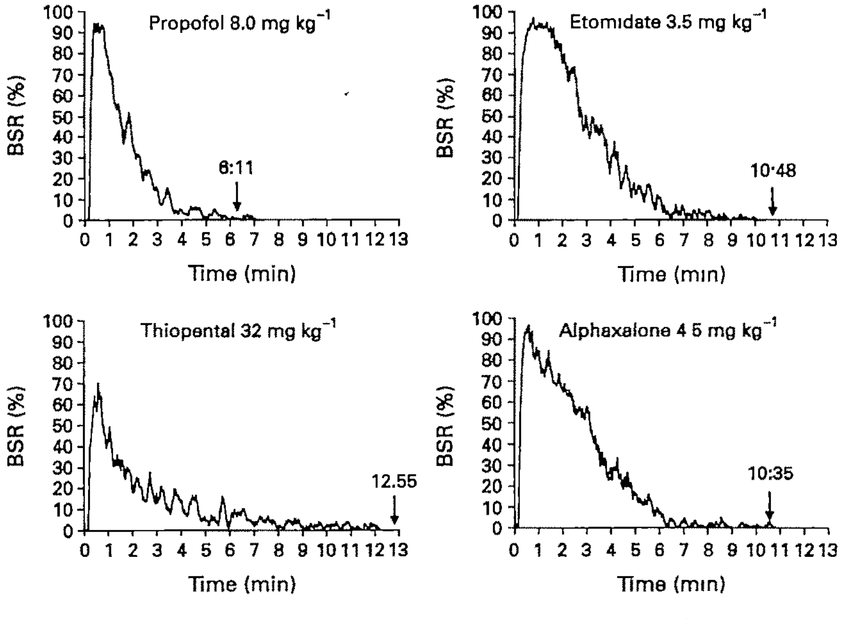

Figure 2 Burst suppression ratio (BSR) after the start of 10-s bolus injections of propofol 8 mg kg^{-1}, etomidate 3.5 mg kg^{-1}, thiopental 32 mg kg^{-1} and alphaxalone 4.5 mg kg^{-1} in four different rats. The arrow in each plot indicates the moment (min:s) when the righting reflex returned.

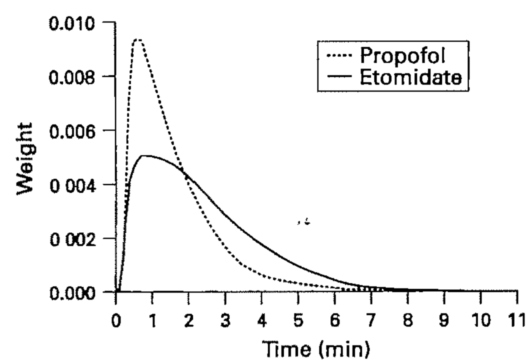

Figure 3 Weighting functions *D* in equation (1) for propofol and etomidate which were used for continuous calculation of the set-point of the closed-loop system. These functions were obtained by averaging the burst suppression ratio (BSR) responses after bolus injections (propofol 8.0 mg kg^{-1}, n=4 and etomidate 3.5 mg kg^{-1}, n=4), smoothing the resulting curves and scaling such that the area under the curve equalled 1.

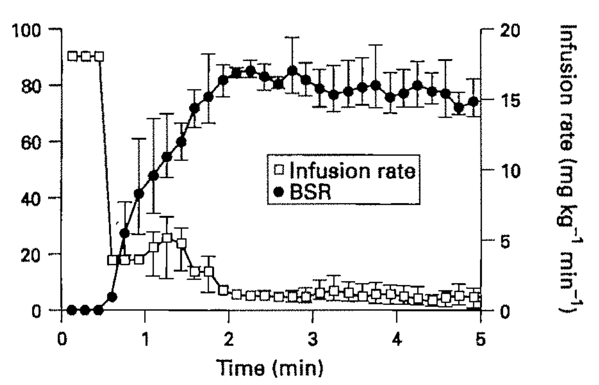

Figure 4 Early response and stabilization of the closed-loop system. Initial changes of the infusion rate and the burst suppression ratio (BSR) during the first 5 min after starting the propofol infusion with a BSR target of 70% are shown as the means of three experiments. Although the infusion rate was adapted every second, for clarity each datum point represents the mean value over 10 s. The error bars indicate the minimum and maximum observed value in the three experiments. Note the constant rates *Iind* and 0.2×*Iind* during the first minute.

90% BSR were mean 0.16 (SD 0.04), 0.22 (0.04), 0.34 (0.03) and 0.48 (0.09) mg $kg^{-1} min^{-1}$. For propofol these values were 0.64 (0.03), 0.88 (0.13), 1.08 (0.17) and 1.70 (0.05) mg kg^{-1} min^{-1}. The infusion rates to maintain steady BSR decreased with time for both drugs. Figure 6 illustrates this decrease over successive 10-min intervals.

With etomidate, the infusion rate decreased until the end of the infusion and declined to approximately 60% of its initial value during the last 10 min. With propofol, an almost constant infusion rate at 80% of its starting value was reached after 40 min.

Figure 7 shows recovery times after the end of infusions. With higher BSR targets, both the time to halving of BSR and the time to regain the righting reflex increased steeply. After closed-loop infusions at 90% BSR, recovery was much slower than after bolus injections that produced high BSR values (>90%, see fig. 2).

The paw withdrawal response was not suppressed (normal) at the 30% BSR target with both drugs in all rats. In the traces at this target in figure 5, a response in the BSR signals to this stimulus can be observed as a transient trough coinciding with a peak in the infusion rate. At 50%, paw withdrawal was weak with propofol and moderate to normal with etomidate, and still present in all animals. At 70% the response with etomidate was weak in two and absent in one of three animals, and absent with propofol in all three animals. At 90% none of the animals responded to either drug.

Discussion

Compared with published definitions of burst suppression detection, our method has improved sensitivity, extending the dynamic range to lower anaesthetic levels. This is demonstrated by the fact that doses well within the advised dosing ranges for i.v. induction of general anaesthesia in rats (e.g. thiopental 30 mg kg^{-1}, alphaxalone 6–9 mg kg^{-1} [18]) produced clearly detectable, drug-characteristic BS responses. Elementary variables of a drug, such as speed of induction of anaesthesia or potency, could be derived from these BSR responses. Their values could be calibrated on traces whereby a maximum specified BSR effect is reached, enabling accurate comparisons between drugs.

Our closed-loop infusion system performed well in maintaining BSR at multiple stable targets with etomidate and propofol. The selected cortical effect (BSR) was reached within the first minutes of the infusion and was maintained accurately until 60 min. Paw stimulation, although intended to measure reflex suppression, also demonstrated the ability of the system to cope with sudden changes in BSR caused by arousal reactions. The system responded well with appropriate alterations in infusion rate and rapidly corrected anaesthesia back to its target.

As our system requires no input values other than those derived easily from bolus injection experiments, it is well suited to test new i.v. anaesthetic compounds of which the pharmacokinetics and pharmacodynamics are unknown. Appropriate testing of a new i.v. anaesthetic would first determine if it can be used for maintaining anaesthesia at specified levels for a prolonged period, and would estimate the required doses. Recovery times after these maintained infusions could be determined and compared with those after bolus injections. Large increases, an order of magnitude larger than seen with propofol or etomidate shown here, would indicate serious, unacceptable accumulation and dominating redistribution of the drug.[2-4]

During stable anaesthesia, established using a closed-loop system, other measures to assess depth of anaesthesia could be tested and cardiorespiratory and other variables could be measured easily. We found that paw withdrawal during propofol anaesthesia was less pronounced than the response during etomidate anaesthesia. This illustrates that at a cortically (EEG) defined level of anaesthesia, suppression of other responses may vary between drugs.

Finally, the system could be used to obtain the pharmacokinetic–dynamic characteristics of a drug. Some important kinetic characteristics of the drug are represented in the infusion rate against time curve,[17] and in the recovery profiles after infusions.[2] If plasma sampling is included, full and flexible

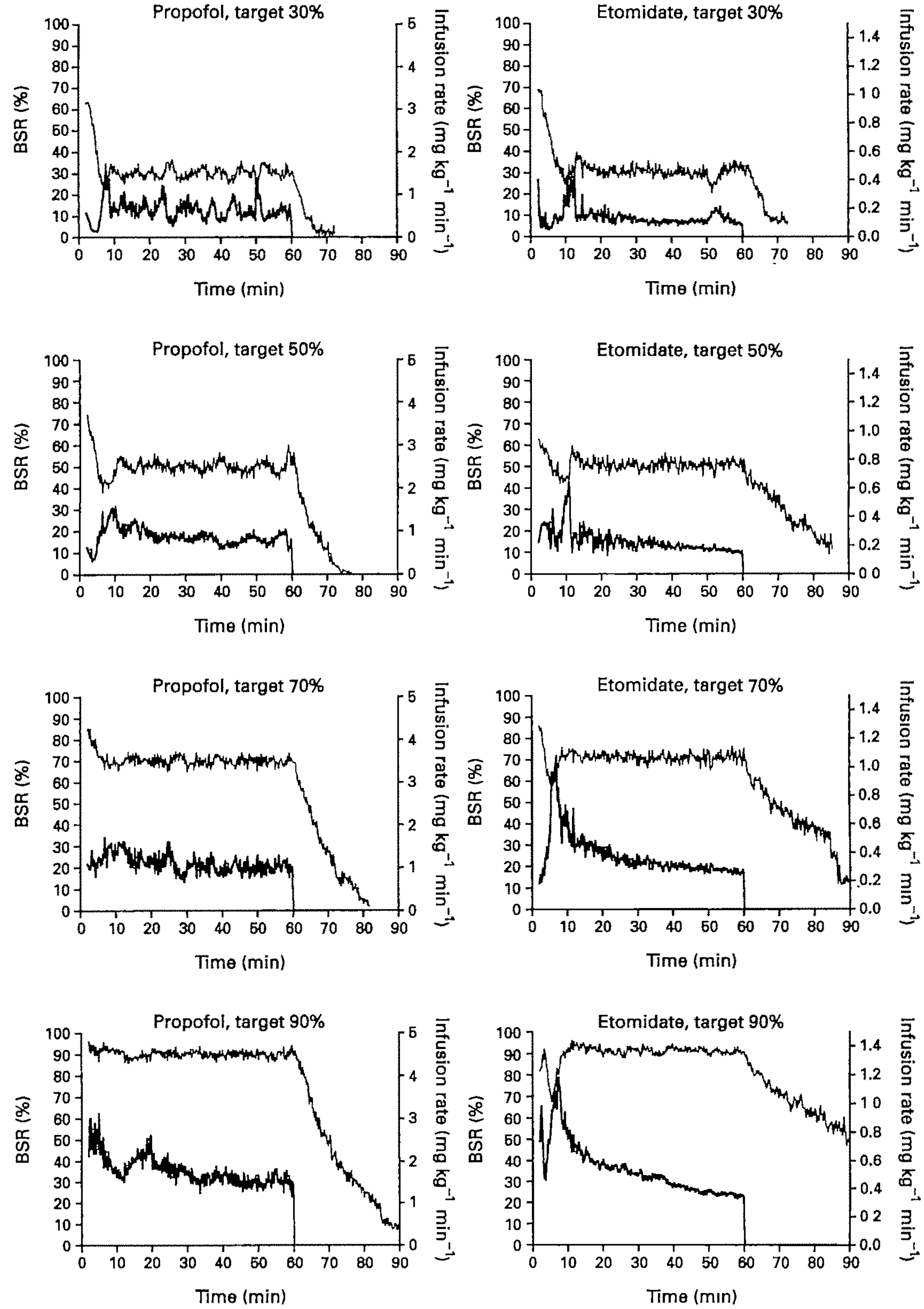

Figure 5 Performance of the closed-loop system over 60 min. Animals were anaesthetized with propofol (left) and etomidate (right) at four different burst suppression targets of 30% (top), 50%, 70% and 90% (bottom). The lower, thick traces are the drug infusion rates and the upper, thin traces the burst suppression ratio (BSR) responses during and after the 60-min infusion period. All traces represent the mean of three animals. For clarity, data from the first 2 min after induction are omitted. Note a transient decrease in BSR as a response to the paw withdrawal measurement at the 50th minute at the 30% target with both drugs

pharmacokinetic–pharmacodynamic modelling is feasible. The design and use of a closed-loop system to render a pharmacokinetic–pharmacodynamic model is the opposite of the traditional approach, where a pharmacokinetic–pharmacodynamic model, known in detail, is incorporated into the design of an open- or closed-loop infusion system.[7 8]

Our system shows that even without detailed information on a drug, excellent closed-loop performance can be achieved. We tested our system with two "short-acting" i.v. anaesthetics which are used clinically for maintenance of anaesthesia in humans. Etomidate and propofol equilibrate moderately fast with the effect site, and both are well described by

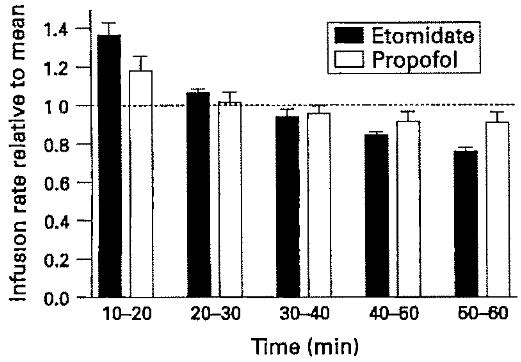

Figure 6 Infusion rate decrement with time during the propofol and etomidate experiments. Infusion rates per 10-min interval are expressed as the fraction of the average rate (broken horizontal line, 1 by definition) during the 10–60-min interval. These fractions at all four BSR targets have been averaged. Error bars represent mean absolute deviations.

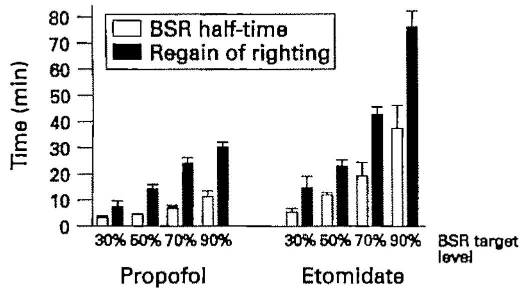

Figure 7 Recovery after 60 min of closed-loop anaesthesia. Time after stopping the infusion for burst suppression ratio (BSR) to decrease to 50% of the BSR target as a measure of EEG recovery, and time to regain the righting reflex as a behavioural measure. Each bar is the mean of three experiments. Error bars represent mean absolute deviations.

three-compartmental models with a relatively fast and dominating first distribution phase.[19] The question arises if our system can also maintain a steady effect with drugs that have either a slower onset or a less favourable distribution–elimination profile. The purpose of the system however is to assist in the selection of new drugs to be used as clinical anaesthetics and one might argue that drugs with inadequate responses should be discarded.

In summary, we have built a closed-loop system for maintenance of stable i.v. anaesthesia in rats and we propose that this apparatus could expedite the appropriate selection and rejection of candidate compounds in an anaesthetic drug development programme. The characteristics of propofol and etomidate might serve as standards in this selection process.

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Steady-state propofol brain:plasma and brain:blood partition coefficients and the effect-site equilibration paradox

S. DUTTA, Y. MATSUMOTO, A. MURAMATSU, M. MATSUMOTO, M. FUKUOKA AND W. F. EBLING

Summary

Based on volume–flow relationships, CNS agents that are highly lipid soluble (log octanol–water partition coefficient >2) are expected to have equilibration half-times ($T_{1/2}\ k_{E0}$) that are proportional to brain solubility. Propofol, the most lipophilic anaesthetic in clinical use, has $T_{1/2}\ k_{E0}$ values of 1.7 and 2.9 min in rats and humans, respectively, compared with an expected value of at least 8 min. As a first step in exploring this discrepancy between observed and predicted values, we determined the steady state brain:plasma and brain:blood partition coefficients in rats after a 4-h infusion of propofol. Brain:plasma and brain:blood partition coefficients were 8.2 (SD 1.6) and 3.0 (0.5), respectively. $T_{1/2}\ k_{E0}$ predictions based on brain: blood partitioning in rats are more in agreement with the observed equilibration half-time, suggesting that drug bound to the formed elements of blood participates in the uptake and transfer of propofol to its effect site. (*Br. J. Anaesth.* 1998; **81**: 422–424).

Keywords: anaesthetics i.v., propofol; solubility, partition coefficients; pharmacodynamics

Propofol (2,6-diisopropyl phenol), a highly lipophilic (log octanol–water partition coefficient ($Kp_{\text{Octanol-Water}}$) 4.33) anaesthetic, exhibits a plasma effect-site equilibration half-time ($T_{1/2}\ k_{B0}$) of 1.7 and 2.9 min in rats[1] and humans,[2] respectively. Based on volume–flow relationships, the equilibration half-time of propofol in brain and apparent effect site would be expected to be proportional to its brain solubility. Paradoxically, the high lipophilicity of propofol suggests a high brain:plasma partition coefficient which should result in an expected $T_{1/2}\ k_{B0}$ of greater than 8 min in rats. As a first step in exploring this discrepancy, we determined the steady state brain:plasma ($Kp_{\text{Brain Plasma}}$) and brain:blood ($Kp_{\text{Brain Blood}}$) partition coefficients in rats. This is the first report of measurement of steady state brain:plasma and brain:blood distribution of propofol in the rat.

Materials and methods

Male Wistar rats chronically instrumented with venous (jugular) and arterial (femoral) catheters were given an infusion of Diprivan (Zeneca Pharmaceuticals) 0.5–0.8 mg h^{-1} for 4 h to achieve target arterial plasma concentrations of 1–2 μg ml^{-1}. This infusion rate produces and maintains a state of light anaesthesia in rats. Arterial blood (0.4 ml) was sampled at 0.5, 1, 2, 3, 3.5 and 4 h. The anaesthetized animals were sacrificed at 4 h by decapitation and the brain was harvested. Body weight and rectal temperature were monitored throughout the study.

Initially only the brain and plasma concentrations of propofol were measured in six animals (study 1). $Kp_{\text{Brain Plasma}}$ determined from these animals was unexpectedly high. This high $Kp_{\text{Brain Plasma}}$ value suggested a $T_{1/2}\ k_{E0}$ value of greater than 8 min compared with an observed value of 1.7 min in rats. Therefore, we performed a second study using six additional rats and the same procedure as in study 1. In the second study, we measured plasma and whole blood, in addition to brain concentrations of propofol.

Propofol concentrations in rat plasma, whole blood and brain were measured by a specific reverse phase HPLC–EC method described previously.[1, 3] Intra- and inter-day variability for plasma and whole blood assays were less than 15%, and for whole brain less than 8% in the 0.25–10 μg ml^{-1} and 1–25 μg g^{-1} concentration ranges, respectively.

Two-way ANOVA was used to test if arterial concentrations (plasma and whole blood) were significantly different at 3, 3.5 and 4 h. A two-tailed *t* test was used to test if $Kp_{\text{Brain Plasma}}$ was different from $Kp_{\text{Brain Blood}}$ ($P<0.05$).

Results

Arterial concentrations were not significantly different at 3–4 h or 3.5–4 h for plasma and whole blood, respectively, indicating that steady state had been achieved by 4 h. As $Kp_{\text{Brain Plasma}}$ values determined at 4 h were not different between the two groups, we report pooled values from 12 rats. $Kp_{\text{Brain Plasma}}$ ($n=12$)

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and $Kp_{\mathrm{Brain\ Blood}}$ (n=6) values (8.2 (SD 1.6) and 3.0 (0.5), respectively) were significantly different.

Discussion

For lipid soluble i.v. anaesthetics, the rate and extent of tissue distribution, and the rate of equilibration between blood and brain are important determinants of the rate of onset, intensity and duration of pharmacological effect. The half-life for effect-site equilibration and turnover is quantitatively summarized as the pharmacokinetic–pharmacodynamic link variable $T_{1/2}\ k_{\mathrm{E0}}$. The brain:plasma solubility ($Kp_{\mathrm{Brain\ Plasma}}$) of propofol is in agreement with its high lipophilicity. However, simultaneous occurrence of high $Kp_{\mathrm{Brain\ Plasma}}$ and rapid effect-site turnover are contrary to our current understanding of how volume–flow relationships determine tissue and effect-site turnover.

A drug must exhibit high lipid solubility to rapidly transfer across the blood–brain barrier. As most i.v. anaesthetics, benzodiazepines and opioids (excluding morphine) are highly lipid soluble ($Kp_{\mathrm{Octanol\text{-}Water}}$ >2), membrane permeability or plasma binding does not appear to limit brain uptake. It is believed that for these drugs, the rate of brain uptake (and time to equilibrium with blood) is determined primarily by regional blood flow. Under these conditions the brain can be envisioned as a well stirred compartment with an apparent volume of distribution (V_{App}) equal to the product of brain weight ($\mathrm{WT_{Brain}}$) and $Kp_{\mathrm{Brain\ Plasma}}$:

$$V_{\mathrm{app}} = Kp_{\mathrm{Brain\ Plasma}} \times \mathrm{WT_{Brain}} \qquad (1a)$$

Alternatively, V_{App} of brain can be calculated relative to whole blood concentrations:

$$V_{\mathrm{app}} = Kp_{\mathrm{Brain\ Blood}} \times \mathrm{WT_{Brain}} \qquad (1b)$$

Clearance (Cl_{Brain}) governing uptake and washout of drug from this well stirred compartment is brain plasma flow (Q_{Plasma}):

$$Cl_{\mathrm{Brain}} = Q_{\mathrm{Plasma}}\ (\mathrm{ml\ min^{-1}\ g^{-1}}) \times \mathrm{WT_{Brain}} \qquad (2a)$$

If drug bound to formed elements and plasma proteins is readily available for parenchymal distribution, then blood flow (Q_{Blood}) becomes operative clearance:

$$Cl_{\mathrm{Brain}} = Q_{\mathrm{Blood}}\ (\mathrm{ml\ min^{-1}\ g^{-1}}) \times \mathrm{WT_{Brain}} \qquad (2b)$$

As with all well stirred systems, the half-time for drug turnover in the compartment should be predicted by the following volume–flow relationship (eqn (3a) or (3b)):

Half-time for brain turnover

$$\approx 0.693 \times \frac{Kp_{\mathrm{Brain\ Plasma}} \times \mathrm{WT_{Brain}}}{(Q_{\mathrm{Plasma}}\ \mathrm{ml\ min^{-1} g^{-1}}) \times \mathrm{WT_{Brain}}} \qquad (3a)$$

or

Half-time for brain turnover

$$\approx 0.693 \times \frac{Kp_{\mathrm{Brain\ Blood}} \times \mathrm{WT_{Brain}}}{(Q_{\mathrm{Blood}}\ \mathrm{ml\ min^{-1} g^{-1}}) \times \mathrm{WT_{Brain}}} \qquad (3b)$$

These principles have been reviewed by Ebling, Wada and Stanski.[4]

Half-time for brain turnover has been found to be highly correlated to effect-site equilibration half-time ($T_{1/2}\ k_{\mathrm{E0}}$) for thiopental[4 5] and propofol.[1] If we assume whole brain distribution kinetics to be indistinguishable from the hypothetical effect-site then for most anaesthetic agents the kinetic–dynamic variable $T_{1/2}$ k_{E0} should reflect tissue turnover and be described by:

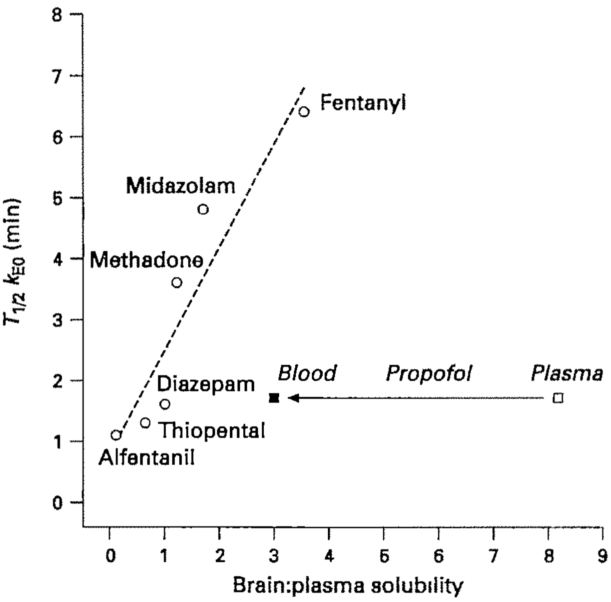

Figure 1 Effect-site equilibration half-time ($T_{1/2}\ k_{\mathrm{E0}}$) *vs* brain: plasma solubility (partition coefficient) for i v. anaesthetics. The broken line is the linear regression fit to the data, excluding propofol. Square symbols are values determined in this study, and circles indicate values from the literature. The arrow indicates the relative reduction in brain solubility of propofol based on steady state whole blood concentrations. Propofol brain:blood solubility is more in agreement with expected effect-site kinetics.

$$T\tfrac{1}{2}k_{\mathrm{eo}} \approx 0.693 \times \frac{Kp_{\mathrm{Brain\ Plasma}}}{Q_{\mathrm{Plasma}}} \qquad (4a)$$

or

$$T\tfrac{1}{2}k_{\mathrm{eo}} \approx 0.693 \times \frac{Kp_{\mathrm{Brain\ Blood}}}{Q_{\mathrm{Blood}}} \qquad (4b)$$

Figure 1 illustrates the linear relationship between brain:plasma solubility and $T_{1/2}\ k_{\mathrm{E0}}$ for lipid soluble benzodiazepines (diazepam[6 7] and midazolam[7 8]), a barbiturate (thiopental[4 5]) and opioids (methadone[9 10], alfentanil[11 12] and fentanyl[11 12]). Propofol, the most lipid soluble anaesthetic based on brain:plasma solubility, exists at the far right of the brain solubility–$T_{1/2}\ k_{\mathrm{E0}}$ relationship. Basing brain solubility on whole blood concentrations places propofol $T_{1/2}\ k_{\mathrm{E0}}$ at a locus more in agreement with the brain solubility–$T_{1/2}\ k_{\mathrm{E0}}$ relationship for other anaesthetics. This finding suggests that all propofol molecules entering the vascular space of the brain, irrespective of whether they are bound to plasma proteins or formed elements of blood, can transfer into parenchyma. This also suggests that propofol is likely to be non-restrictively bound to the formed elements of blood and plasma proteins. (Non-restrictive binding implies that the capillary transit time through the organ must be several times greater than the half-time of dissociation from the formed elements of blood, allowing complete uptake of drug bound to arterial blood elements.)

The rationale for this conclusion is as follows.

Propofol is highly bound to plasma proteins (97%[13]) and is linear in the therapeutic range. Brain:plasma free-water partitioning would be predicted to be 33 times greater than $Kp_{\mathrm{Brain\ Plasma}}$ or approximately 275 (i.e. 8.2/0.03). If only drug that is not bound to plasma proteins or formed elements can participate in blood to brain transfer during capillary transit, then equation (4a) predicts a $T_{1/2}\ k_{\mathrm{B0}}$ value of 4.6 h in rats. (Plasma flow (Q_{Plasma}) = (1–packed cell volume) x blood flow (Q_{Blood}) = 0.55 x Q_{Blood}; rat brain blood flow is 1.25 ml min^{-1} g^{-1}.[4]) By assuming that drug bound to plasma proteins can completely dissociate during capillary transit and fully participate in transfer, similar calculations (eqn (4a)) yield a $T_{1/2}\ k_{\mathrm{B0}}$ of approximately 8.3 min. Both scenarios are untenable as the calculations significantly over-predict the observed $T_{1/2}\ k_{\mathrm{B0}}$. If we assume that drug bound to plasma proteins and formed elements of blood can transfer into parenchyma, then equation (4b) predicts a $T_{1/2}\ k_{\mathrm{B0}}$ value of 1.7 min. Therefore, it appears that whole blood and not plasma or free-water concentration is the thermodynamically relevant species for propofol brain uptake in rats.

Drug transfer across membranes is believed to be governed by the free-water diffusion hypothesis that assumes that free drug concentration is the thermodynamic driving force involved in all kinetic processes. If this hypothesis holds for propofol then this anaesthetic must be non-restrictively bound to plasma proteins and formed elements of blood to allow for complete dissociation during a single circulatory pass through the brain. Non-restrictive binding places an upper limit on the half-time for dissociation of approximately 400 ms. (Rat brain blood flow is 1.25 ml min^{-1} g^{-1} and brain blood volume is 3% of brain weight.[4] Therefore, transit time of blood through brain is approximately 1.5 s (0.03 ml g^{-1}/1.25 ml min^{-1} g^{-1}) in rats. Complete extraction, during a single pass through brain, of total blood load of propofol occurs in approximately four dissociation half-lives. This corresponds to a half-time for dissociation of 0.37 (i.e. 1.5/4) s.)

If the half-time for dissociation into plasma water from formed elements of blood and plasma proteins exceeds capillary transit time, then one must hypothesize that blood–brain transfer does not occur through free-water diffusion. Other transfer mechanisms such as the carrier–collision hypothesis[14] which suggests rapid membrane to membrane or protein to membrane transfer would have to be evoked to explain the observed phenomena. It is unknown if this phenomena occurs for propofol or other highly lipid soluble, low molecular weight compounds. Irrespective of the mechanism, propofol demonstrates extraordinary mobility across physiological boundaries.

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Effects of posture on blood flow diversion by hypoxic pulmonary vasoconstriction in dogs†

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Summary

We used differential excretion of sulphur hexafluoride from the left and right lung to measure blood flow diversion by hypoxic pulmonary vasoconstriction (HPV) in the prone and supine positions in dogs (*n*=9). Gas exchange was assessed using the multiple inert gas elimination technique. Blood flow diversion from the hypoxic (3% oxygen) left lung was mean 70.7 (SD 11.2) % in the supine compared with 57.0 (12.1) % in the prone position ($P<0.02$). The supine position was associated with increased perfusion to low $\dot{V}_A/\dot{Q}$ regions ($P<0.05$). The increased flow diversion with hypoxia in the supine position was associated with more ventilation to high $\dot{V}_A/\dot{Q}$ regions ($P<0.05$). We conclude that flow diversion by hypoxic pulmonary vasoconstriction is greater in the supine position. This effect could contribute to the variable response in gas exchange with positioning in patients with ARDS. (*Br. J. Anaesth.* 1998; **81**: 425–429).

Keywords: lung, blood flow; hypoxia; ventilation, hypoxic response; position, effects; model, dog

Hypoxic pulmonary vasoconstriction (HPV) is one mechanism by which matching of ventilation and perfusion takes place. Pulmonary arteries constrict progressively when exposed to hypoxia.[1] Local oxygen tension in small arterioles (approximately less than 500 μm in diameter) is determined mainly by oxygen tension in alveolar gas. Thus when hypoxic gas enters distal air spaces, vasoconstriction diverts flow to other, presumably better oxygenated, lung regions. The main determinants of this redistribution of flow are, apart from local oxygen concentration, interactions between arterial, alveolar and interstitial pressures, as outlined in the zonal perfusion model of Hughes and colleagues.[2] However, this model has been challenged by a growing number of observations that show large isogravitational perfusion heterogeneity[3–6] and lack of, or minimal, gravitational gradients in the prone position.[5–8] Detailed studies of pulmonary perfusion suggest increased conductance to flow in dorsal lung regions.[9] The reason for this dorsal flow bias could be differences in ventral–dorsal vasoreactivity inherent in the microvasculature[10] or regional differences in branching anatomy.[11]

The tendency of dorsal lung regions to accept more flow enhances gravitational redistribution of perfusion in the supine position. Increased dorsal flow conductance may balance the influence of gravity in the prone position, thus promoting more uniform flow distribution that is typically seen in the prone position.[5,12] We hypothesized that the mechanisms responsible for this asymmetric response to positioning might interact differently with HPV in the prone and supine positions. As many studies show improved gas exchange with prone positioning of patients with ARDS[13–16] or obesity,[17] we speculated that this might result, in part, from more efficient matching by HPV of perfusion to ventilation in the prone position. This notion was explored using a dog split lung model in which the left lung was subjected to hypoxia (3% oxygen), and the right lung ventilated with 100% oxygen for the entire experiment. In this study, we found more hypoxic diversion of blood flow, assessed using the multiple inert gas elimination technique (MIGET), in the supine compared with the prone position.

Materials and methods

ANIMAL PREPARATION AND PHYSIOLOGICAL MEASUREMENTS

The study was approved by the University of Washington Animal Care Committee. We used nine dogs (mean weight 20.8 (SD 1.8) kg). They were fasted overnight but had free access to water. A peripheral vein was cannulated and anaesthesia was induced with pentobarbital 30 mg kg^{-1} i.v. and maintained with intermittent i.v. doses as required (30–90 mg every 20–30 min). The trachea was intubated orally and the lungs ventilated with a tidal volume of 15 ml kg^{-1}. A femoral artery catheter, pulmonary artery catheter via the external jugular vein, and a femoral venous catheter were inserted via peripheral cutdowns. Systemic arterial, pulmonary arterial, pulmonary arterial occlusion and airway pressures were measured continuously and recorded on a Western Graphic Mach 12 data-management system DMS 1000 with Validyne amplifiers (Irvine, CA, USA). Vascular pressures were zeroed to the mid-chest level. Body temperature was maintained at 38±1°C using heating lamps

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and pads. Thermodilution cardiac outputs ($\dot{Q}\mathrm{T}$) were obtained in triplicate (Edward's SAT-2 Cardiac Output Computer, Santa Ana, CA, USA).

A Kottmeier double-lumen endobronchial tube (Les Wilkins Co., Seattle, WA, USA) was inserted via a subcricoid tracheostomy. Complete lung isolation was verified by the absence of air bubbles escaping from one limb of the endobronchial tube when the other was hyperinflated, and the absence of cross-contamination when the lungs were ventilated separately with helium. Both lungs were ventilated synchronously with a Harvard dual-piston ventilator (South Natick, MA, USA) with separate gas breathing systems. The inspired gas mixture was adjusted using a Cameron GF-5 Gas Flowmeter (Port Aransas, TX, USA). Inspired, mixed-expired and end-tidal $P\mathrm{CO}_2$ and $P\mathrm{O}_2$ were measured with a Mass spectrometer (Perkin Elmer, Medical Gas Analyzer Instrumentation Laboratories 1302) and corrected for body temperature. Right and left tidal volumes were set at 9 and 6 ml kg^{-1}, respectively, and were adjusted to yield equal airway pressures of 10–15 cm H_2O. Ventilatory frequency was adjusted to yield normocapnia. The lungs were hyperinflated every 30 min to prevent microatelectasis.

MULTIPLE INERT GAS ELIMINATION TECHNIQUE

The multiple inert gas elimination technique (MIGET) was used to assess pulmonary gas exchange[18 19] and the fraction of blood flow to the left and right lungs.[20] A solution of six inert gases (sulphur hexafluoride, ethane, cyclopropane, halothane, diethyl ether and acetone) dissolved in 5% dextrose was infused into the femoral vein catheter at a rate of 3 ml min^{-1} for 1 h before starting any measurements. Inert gas partial pressures were measured in duplicate blood samples collected simultaneously from the pulmonary and femoral arteries and in mixed expired gas. Exhaled gas specimens were maintained at >40°C before analysis to avoid condensation and loss of high solubility gases.

Concentration of inert gases were measured using a gas chromatograph (Varian 3300, Walnut Creek, CA, USA) equipped with a flame ionization detector and an electron capture detector. The gas extraction method of Wagner, Naumann and Laravuso[21] was used to determine the concentration of inert gases in the blood samples.

STUDY PROCEDURE

Before beginning the study, the animals were "primed" with 3–4 hypoxic challenges. After demonstration of a stable HPV response by consistent increases in mean pulmonary artery pressure and stable arterial blood-gas tensions with left lung hypoxia, the study began. The right lung was ventilated with an $F\mathrm{I}_{\mathrm{O}_2}$ of 1.0 throughout the study. The left lung was ventilated with an $F\mathrm{I}_{\mathrm{O}_2}$ of 1.0 (hyperoxia) or 0.03 (hypoxia) in random order. Inspired carbon dioxide ($F\mathrm{I}_{\mathrm{CO}_2}=0.03$) was added to the left lung inspired gas mixture during hypoxia, and to both lungs ($F\mathrm{I}_{\mathrm{CO}_2}=0.01$–$0.02$) during hyperoxia to prevent cyclical variations in the HPV response caused by alveolar hypocapnia. Animals were studied in the supine and prone positions in random order. Blood-gas tensions, collection of mixed expired gas samples and haemodynamic measurements were obtained after a stabilization period of 20 min in each phase.

CALCULATIONS AND STATISTICAL ANALYSIS

Pulmonary blood flow to each lung was calculated by the Fick principle for the inert gas with the lowest solubility in blood, sulphur hexafluoride (SF_6):

$$\dot{Q}_R = (\dot{V}_R x P_R(\exp)_{SF6})/\lambda_{SF6}\ (P(v)_{SF6} - P(a)_{SF6})$$

$$\dot{Q}_L = (\dot{V}_L x P_L(\exp)_{SF6})/\lambda_{SF6}\ (P(v)_{SF6} - P(a)_{SF6})$$

where $\dot{Q}_R$ and $\dot{Q}_L$=right and left lung blood flow; $\dot{V}_R$ and $\dot{V}_L$=right and left lung minute ventilation; $P_R(\exp)_{SF6}$ and $P_L(\exp)_{SF6}$=partial pressure of SF_6 in mixed expired gas from the right and left lung; λ_{SF6}=Ostwald blood-gas partition coefficient of SF_6; $P(v)_{SF6}$ and $P(a)_{SF6}$=partial pressure of SF_6 in mixed venous and arterial blood. Blood flow to each lung was expressed as a fraction of total pulmonary blood flow. Left lung blood flow diversion during hypoxia was calculated as $(\dot{Q}_{\mathrm{hyperoxia}} - \dot{Q}_{\mathrm{hypoxia}})/\dot{Q}_{\mathrm{hyperoxia}}$ and expressed as percent.[22]

Concentrations of the six inert gases in mixed expired gas, pooled from both lungs, were used to assess changes in the ventilation/perfusion ($\dot{V}\mathrm{A}/\dot{Q}$) distributions predicted by the 50-compartment model of Wagner, Saltzman and West, and Evans and Wagner.[18 19] This model considers the lung to consist of 50 homogeneous compartments arranged in parallel, each with $\dot{V}\mathrm{A}/\dot{Q}$ values evenly spaced on a logarithmic scale. Inert gas shunt, deadspace, mean $\dot{V}\mathrm{A}/\dot{Q}$ ratios of $\dot{V}\mathrm{A}$ and $\dot{Q}$ distributions, percentage of $\dot{Q}$ to low $\dot{V}\mathrm{A}/\dot{Q}$ units ($\dot{V}\mathrm{A}/\dot{Q}$ ratio 0.005–0.1), and percentage of $\dot{V}\mathrm{A}$ to high $\dot{V}\mathrm{A}/\dot{Q}$ units ($\dot{V}\mathrm{A}/\dot{Q}$ ratio 10–100) were calculated from the 50-compartment model.

Data were analysed by two-factor ($F\mathrm{I}_{\mathrm{O}_2}$ and position) within-subjects analysis of variance. Significant differences determined from analysis of variance were analysed by calculating the least significant difference. Data are expressed as mean (SD). $P<0.05$ was considered significant.

Results

Right and left airway pressures, and left and right end-tidal carbon dioxide concentrations were not different between the conditions; the latter were within normal limits in both lungs (4.5–5.7%). There were no significant changes in $P\mathrm{a}_{\mathrm{CO}_2}$ and $P\mathrm{a}_{\mathrm{O}_2}$; $P\bar{\mathrm{v}}_{\mathrm{O}_2}$ did not change with position but decreased during hypoxia (table 1).

Mean pulmonary artery pressure increased significantly with hypoxia ($P<0.01$) but did not differ between positions when analysed by two-factor ANOVA. Pulmonary artery occlusion pressure and systemic artery pressure were unaffected by hypoxia but systemic artery pressure changed significantly with position. Cardiac output did not differ significantly between the conditions (table 1).

The proportion of total pulmonary perfusion flowing to the left lung during hyperoxia was not significantly different between the prone and supine positions (0.40 (0.05) and 0.39 (0.05), respectively). Left lung blood flow diversion by hypoxia was 57.0

Table 1 · Blood-gas tensions and haemodynamics (mean (SD)). ***$P<0.001$ *vs* hyperoxia; †$P<0.05$, ††$P<0.01$ *vs* prone posture with same $F\text{I}_{O_2}$

	Hyperoxia		Hypoxia	
	Prone	Supine	Prone	Supine
Arterial oxygen tension (mm Hg)	604 (21)	586 (30)	221 (97)***	259 (94)***
Arterial carbon dioxide tension (mm Hg)	38 (2)	39 (6)	39 (4)	42 (5)
Mixed venous oxygen tension (mm Hg)	78 (14)	72 (7)	61 (9)***	60 (7)***
Mean pulmonary artery pressure (mm Hg)	18 (4)	16 (4)	23 (5)***	20 (4)***
Pulmonary artery occlusion pressure (mm Hg)	7 (1)	12 (5)†	8 (4)	11 (3)
Mean systemic artery pressure (mm Hg)	147 (13)	125 (13)††	149 (11)	120 (11)††
Thermodilution cardiac output (litre min^{-1})	4.6 (1.6)	3.7 (1.0)	4.4 (1.5)	3.8 (0.8)

Table 2 Gas exchange variables (mean (SD)). $V\text{A}/Q$ = ventilation perfusion ratio. **$P<0.01$, ***$P<0.001$ *vs* hyperoxia, †$P<0.05$ *vs* prone posture with the same $F\text{I}_{O_2}$

	Hyperoxia		Hypoxia	
	Prone	Supine	Prone	Supine
Mean $V\text{A}/Q$ of the perfusion distribution	0.88 (0.19)	0.75 (0.16)	0.67 (0.19)**	0.61 (0.18)**
Mean $V\text{A}/\dot{Q}$ of the ventilation distribution	0.82 (0.35)	0.96 (0.34)	1.36 (0.33)***	1.37 (0.29)***
Shunt (%)	0.6 (0.9)	1.7 (1.3)	1.2 (1.5)	1.6 (1.9)
Perfusion to $\dot{V}\text{A}/\dot{Q}$ = 0.005–0.1 (%)	0.7 (1.6)	4.1 (3.4)†	1.0 (1.8)	5.5 (3.8)†
Ventilation to $V\text{A}/Q$ = 10–100 (%)	2.3 (3.1)	3.1 (3.4)	7.5 (3.9)***	13.8 (7.8)***†
Deadspace (%)	39.0 (5.0)	40.7 (6.5)	41.2 (2.4)	38.9 (6.3)

(12.1) % in the prone and 70.7 (11.2) % in the supine position ($P<0.02$, fig. 1). Inert gas shunt and deadspace did not change between conditions (table 2). Perfusion to regions with low $\dot{V}\text{A}/\dot{Q}$ ratios was larger in the supine than in the prone position ($P<0.05$), but there was no significant influence of $F\text{I}_{O_2}$. Ventilation to regions with high $\dot{V}\text{A}/\dot{Q}$ ratios during hypoxia was higher in the supine than in the prone position ($P<0.05$, table 2).

Discussion

The important finding of this study was that redistribution of pulmonary blood flow by hypoxic vasoconstriction was more effective in the supine than in the prone position. Before considering the implications of these results, we discuss some of the limitations of the methods used in our experiment.

METHODOLOGICAL ISSUES

We used dogs to examine the hypothesis that the HPV response was position-dependent and might contribute to improved gas exchange in patients nursed in the prone position. Dogs are large enough to allow for invasive instrumentation and their HPV response has been characterized in great detail.[22–24] A major drawback is that dogs depend more on collateral ventilation than HPV in maintaining ventilation–perfusion matching.[25] However, it is likely that the basic mechanisms that determine flow diversion by HPV are similar in humans and dogs, as suggested by work showing marked similarity across different species.[23 24 26 27]

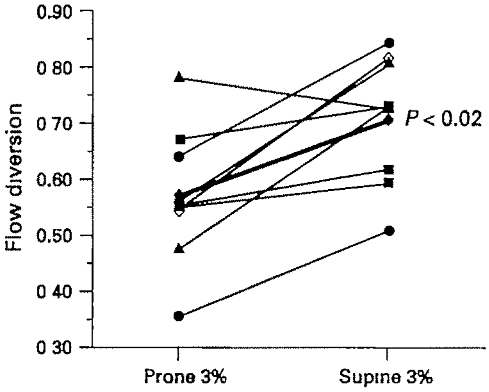

Figure 1 Individual effects of posture on blood flow diversion by left lung hypoxia (3% oxygen). Mean values are connected by a thick line.

We measured blood flow to each lung by applying the Fick principle to the differential excretion of SF_6. This technique was found previously to provide an accurate non-invasive measure of pulmonary blood flow compared with invasive electromagnetometry.[20 28] Retention and excretion data from all six inert gases were used to describe the gas exchange function of the lungs according to the model of Wagner, Saltzman and West, and Evans and Wagner.[18 19]

POSITION RELATED EFFECTS ON HAEMODYNAMIC STATE

Higher mean pressures in the pulmonary and femoral artery were recorded in the prone compared with the supine position. Similar results, with higher systemic arterial pressure in the prone position, have been reported in numerous investigations, including studies in human subjects.[13–15 29–32] The position-associated changes in vascular pressures could be explained in part by failure of the mid-chest level to reflect the true zero reference point in both positions. However, this is unlikely to be the sole mechanism as the use of a catheter in the right atrium as the true zero reference point still produced higher systemic pressure readings in the prone compared with the supine position in anaesthetized dogs.[30] We are not aware of any data that could shed light on the mechanisms responsible for these effects of position on haemodynamic state. It is possible that the heart was restricted by the lungs and its own weight in the supine position. It is equally likely that the prone position was associated with increased stimulation of the larynx and the airways by the tracheal tube, and hence increased sympathetic tone.

EFFECTS OF POSTURE ON BLOOD FLOW DIVERSION AND GAS EXCHANGE

The hypoxic left lung received a smaller fraction of cardiac output in the supine than in the prone position. Flow diversion by hypoxic vasoconstriction is an adaptive mechanism aimed at preserving gas exchange by directing perfusion away from lung segments with hypoxic gas. The efficiency of this response is influenced by the relative sizes of the hypoxic and hyperoxic parts of the lung.[22] The intensity of the response is a function of both alveolar and mixed venous oxygen tensions,[24 26] and it is also influenced by pH and carbon dioxide tension.[33] These factors were balanced between the prone and supine positions in our experiment, and the fraction of cardiac output to the left lung was similar in both positions, suggesting that the difference in flow diversion was caused by change in position. Flow diversion in the supine position was similar to previously published work,[22 28] although direct comparison with other studies is of limited interest because of the numerous factors that influence the response.

The factors responsible for reduced flow diversion in the prone compared with the supine position were not addressed specifically in our study. One mechanism, stated previously, is changes in haemodynamic state, particularly the increase in cardiac output that we and others have observed in the prone position. The results of Domino, Hlastala and Cheney are especially relevant in this respect.[28] In that study, cardiac output was increased by 85% using an external arteriovenous fistula during left lung hypoxia ($F_{I_{O_2}}$=0.04) in supine dogs. The increase in blood flow was accompanied by a decrease from 63% to 48% in left lung hypoxic blood flow diversion. The results from that study suggest that the minute position-related changes in haemodynamic state that we observed cannot alone account for the posture-dependent alterations in flow diversion. Although speculative, it is possible that the asymmetry of the pulmonary circulation that normally balances the influence of gravity in the prone position[11] could account for the larger flow diversion in the supine position. The increased conductance to perfusion in dorsal lung regions[9] may work in concert with gravity by facilitating flow diversion in the supine position.

Data from retention and excretion of inert gases showed a significant increase in the fraction of ventilation to regions with high $\dot{V}_A/\dot{Q}$ ratios (10–100) during hypoxia, which is consistent with diversion of blood flow away from hypoxic lung regions. The increase in ventilation to these high $\dot{V}_A/\dot{Q}$ regions was significantly greater in the supine than in the prone position. This would normally be associated with less efficient gas exchange. However, it occurred under the conditions of the present experiment with split lungs, indicative of more effective separation of perfusion from ventilation in the supine than in the prone position. This observation is in agreement with perfusion data showing more efficient flow diversion in the supine position.

RELATIONSHIP TO THE CLINICAL SETTING

The split lung model can provide some valuable insights into the mechanisms that influence flow diversion by HPV, but cannot serve as a complete model of the complicated effects of HPV in diffuse lung pathology (i.e. ARDS). However, if the structure of the fractally branching pulmonary vasculature[11 34] plays a role in the observed effect, it is plausible that the same position-dependent influence exists on a smaller scale within each lung, with similar effects on the efficiency of regional gas exchange. This could have implications for patient care, among which posture-dependent effects of drugs that influence HPV can be expected. Less efficient flow diversion in the prone position may offset the beneficial influence of prone positioning on distribution of ventilation in ARDS, and thus explain why improvement in arterial oxygenation in the prone position is variable, and sometimes non-existent.[16]

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Effects of etomidate, propofol and thiopental anaesthesia on arteriolar tone in the rat diaphragm†

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Summary

We have assessed, by intravital microscopy in rats, the effects of different anaesthetics on diaphragmatic arteriolar diameter. Rats were anaesthetized with etomidate, propofol or thiopental (groups E, P and T, respectively) and the diameters of the arterioles were measured sequentially at baseline and after topical application of either mefenamic acid (MA, 20 μmol litre^{-1}) or Nω-nitro-L-arginine (NNA, 300 μmol litre^{-1}), inhibitors of prostaglandins and nitric oxide, respectively. In group E, baseline arteriolar diameters were significantly higher than those in the two other groups ($P<0.01$). MA and NNA induced significant constriction in the three groups ($P<0.001$). However, whereas constriction induced by NNA was similar in the three groups, constriction induced by MA was significantly higher in group E compared with groups P and T ($P<0.05$). We conclude that diaphragmatic arteriolar diameters in rats were greater during etomidate than during thiopental or propofol anaesthesia. This phenomenon may be mediated by prostaglandins. (*Br. J. Anaesth.* 1998; **81**: 430–435).

Keywords: muscle skeletal, diaphragm; anaesthetics i.v., etomidate; anaesthetics i.v., propofol; anaesthetics i.v., thiopental; rat

The performance of respiratory muscles is tightly coupled to blood flow. Thus recent studies have indicated that mechanical hyperperfusion of the diaphragm partially delays the development of diaphragmatic fatigue[1] and reverses the loss of force-generating capacity induced by repetitive diaphragmatic contractions.[2] Regulation of diaphragmatic blood flow is dependent on the tone of diaphragmatic microvessels, which can in turn be modulated by different pharmacological agents. I.v. anaesthetics can modulate diaphragmatic microvascular tone. Indeed, during induction and recovery from anaesthesia, the diaphragm may have to cope with a transient increase in the work of breathing, as a result of changes in airways resistance.[3] Therefore, it may be relevant to assess the effects and mechanism(s) underlying the actions of i.v. anaesthetics on diaphragmatic microvascular tone.

Previous studies in different vascular beds demonstrated that microvascular tone and reactivity are altered by i.v. anaesthetics, mainly in the small arterioles.[4–6] These changes are tissue-specific[7] and can involve release of different endogenous vasoactive mediators, such as prostaglandins or nitric oxide, or both.[4 8] However, diaphragmatic and non-diaphragmatic microcirculation were frequently studied under barbiturate anaesthesia.[9–14] The effects of other i.v. anaesthetics are poorly documented.

Asher and co-workers[4] observed *in vivo* in a cremaster model that etomidate dilated precapillary arterioles more than pentobarbital. This dilation was related to release of prostaglandins. Holzmann and co-workers[15] investigated the microcirculatory effects of propofol. In this study in the dorsal skinfold chamber of the hamster, the authors showed that a bolus dose of propofol dilated arterioles and collecting venules. However, no attempt was made to identify the mechanism(s) responsible for these effects. Furthermore, no study has compared the effects of etomidate and propofol anaesthesia on the microcirculation.

Therefore, we performed a comparative study of the effects of etomidate, propofol and thiopental on the microcirculation of the diaphragm. We investigated specifically, by intravital microscopy in rats, the effects of etomidate, propofol and thiopental on diaphragm arteriolar diameters and involvement of prostaglandins and nitric oxide on the maintenance of arteriolar diameters by these anaesthetic agents.

Materials and methods

Male Sprague–Dawley rats (Charles River France Inc.), 100–120 g, were used. All rats were housed individually, acclimatized to a 12-h light–dark cycle, and maintained on Purina rat chow and tap water *ad libitum* for 5 days before the study. The study met the recommendations of French law (Ministère des Affaires Sociales et de la Solidarité Nationale).

The animals were anaesthetized by inhalation of diethyl ether in an anaesthetic chamber and placed supine on a rodent operating table (Harvard Apparatus, MA, USA), placed over a machining table (Wolfcraft T N° 3060, Germany) to allow the animal preparation to be moved in two directions. Anaesthesia was maintained with 3% diethyl ether

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using a small face mask until a tracheotomy was performed. After tracheotomy, the animals' lungs were ventilated mechanically throughout the study with a 50:50 mixture of oxygen and nitrogen, ventilatory frequency 80 bpm and tidal volume 1.3 ml via a rodent ventilator (Ugo Basile Apparatus Inc., Italy). Body temperature was monitored continuously with a rectal probe and maintained constant at 36.5–37.5°C using a heat lamp and a heating pad (Harvard Apparatus Inc., MA, USA).

The left carotid artery was cannulated for continuous measurement of systemic arterial pressure using a Statham P23XL transducer (Spectramed Ltd., Coventry, UK). A second catheter was placed in the right jugular vein to administer 0.9% sterile NaCl 3 ml kg^{-1} h^{-1}. A third 25-gauge catheter was placed into the left jugular vein for continuous administration of i.v. anaesthetics.

DIAPHRAGM PREPARATION

The model has been described in detail previously.[12] Briefly, bilateral thoracotomy was performed in the fifth intercostal space, avoiding the sternum. The diaphragm was separated carefully from the lungs and from the mediastinal tissues, and the phrenic nerves were sectioned. The abdomen was opened via a midline laparotomy. This was followed by a transversal incision to expose and place the costal diaphragm in a perpendicular position relative to the body of the animal. The abdominal organs were covered with cotton sheets moistened with warm saline solution. The animal was placed in the head-down position and the abdominal viscera were immobilized by covering with a Cellophane wrap fixed to the operating table.

Irrigation of the abdominal side of the diaphragm began immediately after exposure via a microperforated hose placed gently on the top of the abdominal surface at a flow rate of 500 ml h^{-1}, with a modified Krebs–Henseleit solution containing (mmol litre^{-1}): NaCl 118, KCl 5.9, $CaCl_2$–$2H_2O$ 2.5, $MgSO_4.7H_2O$ 0.5, $NaHCO_3$ 28 and glucose 10. This solution was maintained at a constant temperature of 37.5°C. By bubbling the solution with a 5% carbon dioxide–95% nitrogen gas mixture, pH, Pa_{O_2} and Pa_{CO_2} of the solution were fixed at 7.41±0.06, 3.1±0.2 kPa and 5.5±0.05 kPa, respectively. These values were obtained after the first 15 min of bubbling. pH was monitored continuously with a pH meter (PM83, Radiometer, Copenhagen, Denmark). $P\text{O}_2$ and $P\text{CO}_2$ were measured twice during the study. Pancuronium 4 μmol litre^{-1} was added to this solution to prevent muscle fasciculations. This dose of pancuronium had no systemic effects and no effects on microcirculatory variables.[16]

The muscle was transilluminated using a 150-W tungsten halogen lamp connected to a fibreoptic cool light microprobe introduced gently into the thorax by the left thoracotomy. The diaphragmatic microcirculation was seen by observing the abdominal side of the muscle with a modified Leitz microscope which can be placed in a position parallel to the area of the muscle under observation. The image, magnified by a x20 long-distance objective, was projected into a CCD video camera (Sony DXC-101P) connected to a videotape recorder (Sony VO-9600 P) and a video monitor (Sony PVM-1371 QM).

We studied changes in the diameter of the arteriolar branches arising from the internal mammary and intercostal arteries. Arterioles were identified by their relative locations in the network according to morphological criteria derived from Zweifach and Lipowski.[17] Vessels selected for study were second- and third-order arterioles (A2 and A3, respectively). Depending on the geometry of the part of the network studied, 1–3 arterioles of each order were examined in each animal. Arteriolar diameters were measured by playback analysis of the video record, directly off the monitor screen, using the technique of Intaglietta and Tompkins[18] and a dimension measurement device (IPM 303 Dimension Analyser, San Diego, CA, USA).

Just after placement of the catheters, administration of diethyl ether was stopped and the animals (n=60) were allocated randomly to one of three groups according to the i.v. anaesthetic used: etomidate (group E, 23 rats), propofol (group P, 19 rats) or thiopental (group T, 18 rats). Initial doses were etomidate 8 mg kg^{-1} h^{-1}, propofol 40 mg kg^{-1} h^{-1} and thiopental 60 mg kg^{-1} h^{-1}. After 15 min of infusion, these doses were adjusted to maintain mean arterial pressure greater than 90 mm Hg and to suppress the response to painful stimuli (tail pinching). After a 30-min stabilization period, when the rats were at a stable surgical level of anaesthesia and when arterial pressure and heart rate did not fluctuate, surgical preparation of the diaphragm was performed. Then, up to two A2 and three A3 arterioles in the same preparation were selected and their diameters measured (basal diameter). After this measurement, each group was allocated randomly to one of three subgroups according to topical application on the diaphragm of either Krebs solution alone (subgroup C), Krebs solution containing mefenamic acid 20 μmol litre^{-1}, a selective inhibitor of prostaglandin synthesis[19] (subgroup MA) or Krebs solution containing Nω-nitro-L-arginine (NNA) 300 μmol litre^{-1}, a potent inhibitor of nitric oxide synthesis[20 21] (subgroup NNA). After 20 min of irrigation by one of these solutions, the diameter of the selected arterioles was reassessed (diameter after inhibitor). After this, adenosine 1 mmol litre^{-1} was applied topically to measure maximal arteriolar diameter.

Etomidate (Janssen Laboratories, Boulogne-Billancourt, France) was dissolved in propylene glycol (35%volume/volume in saline). Propofol in aqueous emulsion (1% propofol, 10% soya bean oil, 2.25 glycerol and 1.2% egg phosphatide) was supplied by Zeneca Pharma France (Cergy, France). Thiopental (Na salt) was obtained from Specia Rhône-Poulenc Rohrer Laboratories (Paris, France). Mefenamic acid, NNA and adenosine were obtained from Sigma Chemical Co (St Louis, MO, USA). Mefenamic acid was dissolved in sodium bicarbonate 1 mg ml^{-1} and diluted to the final concentration with Krebs solution. NNA and adenosine were dissolved directly in Krebs solution by stirring at room temperature. Drugs solutions were prepared fresh daily.

STATISTICAL ANALYSIS

All results are given as mean (SEM). Data obtained for the three groups were analysed by analysis of variance. When the overall comparison was significant,

Table 1 Mean (SEM) arterial pressure (MAP, mm Hg) and heart rate (HR) before and after administration of etomidate (group E), propofol (group P) or thiopental (group T). No significant differences

	Group E	Group P	Group T
Before administration			
MAP	97 (2)	96 (1)	95 (2)
HR	434 (9)	427 (10)	413 (10)
After administration			
After preparation			
MAP	102 (2)	95 (1)	94 (1)
HR	415 (7)	395 (10)	407 (11)
At end of procedure			
MAP	100 (2)	98 (2)	96 (1)
HR	428 (6)	406 (8)	421 (10)

Table 2 A2 diameters (mean (SEM)) in the etomidate (E), propofol (P) and thiopental (T) groups. Subgroups C, MA and NNA=preparations superfused with Krebs solution alone, or Krebs solution containing mefenamic acid 20 µmol litre^{-1} or Nω-nitro-L-arginine 300 µmol litre^{-1}, respectively. n=number of arterioles. Significantly different from basal diameter, *$P<0.05$, **$P<0.01$; †significantly different from other groups ($P<0.05$)

	n	Basal diameter	Diameter after inhibitor	Maximal diameter
Group E				
Subgroup C	12	58.5 (4.6)†	60.3 (3.9)†	58.4 (4.6)
Subgroup MA	12	59.6 (4.9)†	46.6 (3.2)**	63.9 (4.1)
Subgroup NLA	11	60.5 (3.7)†	49.2 (4.8)**	61.4 (5.1)
Group P				
Subgroup C	11	46.5 (3.3)	45.7 (2.9)	58.1 (4.3)**
Subgroup MA	10	50.1 (3.1)	47.6 (3.7)*	59.3 (4.8)**
Subgroup NLA	14	42.6 (4.2)	30 (2.5)**	60.6 (4.6)**
Group T				
Subgroup C	13	41.6 (3.3)	40.9 (3.6)	53.6 (5.1)**
Subgroup MA	11	46.2 (3.5)	42.4 (3.1)*	60 9 (4.5)**
Subgroup NLA	12	44.5 (3.2)	36.4 (2.3)**	60.5 (3.5)**

individual comparisons were made using Duncan's multiple range test. Significance was accepted at $P<0.05$.

Results

Duration of ether inhalation was similar in groups E, P, and T (29 (2), 31 (2) and 30 (2) min, respectively) and the inhaled concentration was always the same (3 vol%). Mean doses of anaesthetics administered were: etomidate 8.8 (0.7) mg kg^{-1} h^{-1}, propofol 48.7 (2.6) mg kg^{-1} h^{-1} and thiopental 68.5 (6.0) mg kg^{-1} h^{-1}. Infusion volume was similar in the three groups. Mean arterial pressure and heart rate during the study were similar in the three groups (table 1).

Mean Pa_{O_2}, Pa_{CO_2} and pH at the end of the study were 38.2 (5.2), 36.0 (4.0) and 37.0 (6.4) kPa, 3.7 (0.4), 4.3 (0.5) and 4.4 (0.4) kPa, and 7.37 (0.04), 7.36 (0.02), 7.38 (0.06) in groups E, P and T, respectively (ns).

A2 DIAMETERS

Table 2 shows the A2 diameters in the groups and subgroups. Basal and maximal diameters (diameters after application of adenosine 1 mmol litre^{-1}) were similar in the three subgroups of each group. Consequently, to compare the effects of the different anaesthetic agents on arteriolar diameter, data from the three subgroups of each group were pooled. Basal diameters were similar in groups P and T (45.9 (2) µm, n=35 and 43.9 (2) µm, n=36, respectively). In contrast, basal A2 diameters in group E were significantly greater than those in groups P and T (59.5 (3) µm, n=35; $P<0.01$). Maximal diameters were not different between the three groups: 61.2 (3) µm, 59.4 (3) µm and 58.2 (3) µm for groups E, P and T, respectively. In groups P and T, basal diameters were significantly less than maximal diameters ($P<0.01$). In contrast, in group E, basal diameters were similar to maximal diameters.

After 20 min of superfusion with either mefenamic acid or NNA, significant constriction of diaphragmatic A2 diameters was observed in the three groups ($P<0.05$), whereas no significant change in A2 diameter was observed after superfusion of the muscle with Krebs solution alone (fig. 1). However, whereas the constriction induced by NNA was similar in the three groups (ns), constriction induced by mefenamic acid was significantly higher in group E compared with groups T and P ($P<0.05$).

A3 DIAMETERS

Table 3 shows the A3 diameters in the groups and subgroups. As basal and maximal diameters were similar in the three subgroups of each group, these data were pooled, as for the A2 vessels. Basal diameters were similar in groups T and P (35.4 (1.5) µm, n=39 and 39.3 (2.1) µm, n=37, respectively). In contrast, basal A3 diameters in group E were significantly greater than those in groups P and T (45.5 (1.9) µm, n=45; $P<0.01$). Maximal diameters were similar in the three groups: 45.3 (2.1) µm, 52.4

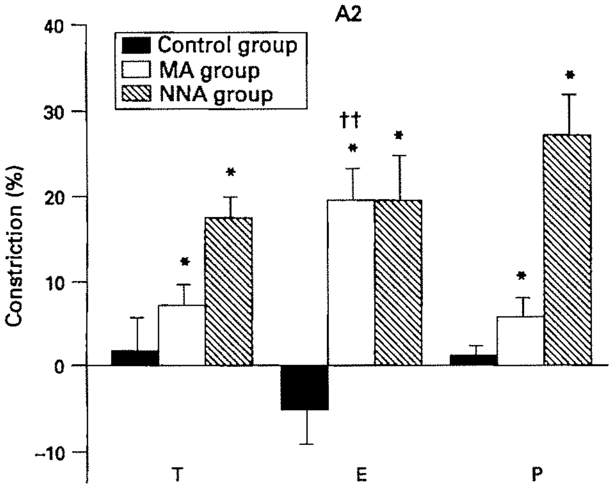

Figure 1 Vasoconstriction (%) of second-order diaphragmatic arterioles (A2) in the different subgroups (Krebs solution alone (subgroup C), Krebs solution containing mefenamic acid 20 μmol litre^{-1}, a selective inhibitor of prostaglandin synthesis[19] (subgroup MA) or Krebs solution containing Nω-nitro-L-arginine (NNA) 300 μmol litre^{-1}, a potent inhibitor of nitric oxide synthesis[20 21] (subgroup NNA)) of the thiopental, etomidate and pentobarbital groups (T, E, and P respectively). Vasoconstriction was calculated as basal diameter minus the diameter after inhibitor divided by basal diameter. *$P<0.05$ *vs* basal diameter; ††$P<0.01$ *vs* MA in groups T and P.

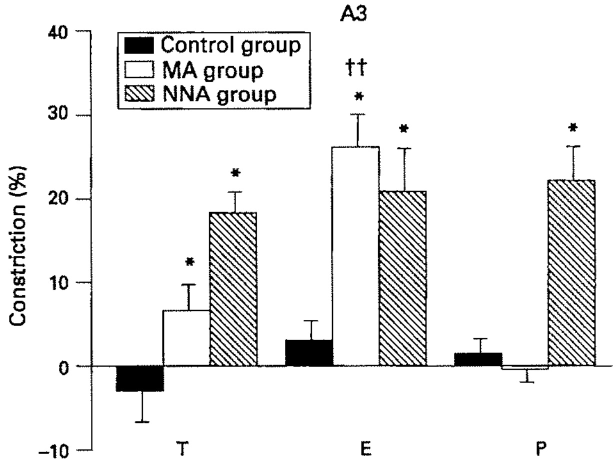

Figure 2 Vasoconstriction of third-order diaphragmatic arterioles (A3) in the different subgroups (Krebs solution alone (subgroup C), Krebs solution containing mefenamic acid 20 μmol litre^{-1}, a selective inhibitor of prostaglandin synthesis[19] (subgroup MA) or Krebs solution containing Nω-nitro-L-arginine (NNA) 300 μmol litre^{-1}, a potent inhibitor of nitric oxide synthesis[20 21] (subgroup NNA)) of the thiopental, etomidate and pentobarbital groups (T, E, and P respectively). Vasoconstriction was calculated as basal diameter minus the diameter after inhibitor divided by basal diameter. *$P<0.01$ *vs* basal diameter; ††$P<0.001$ *vs* MA in groups T and P.

(2.4) μm and 47.9 (1.9) μm for groups T, E and P, respectively. In groups P and T, basal diameters were significantly less than maximal diameters ($P<0.01$). In contrast, in group E, basal diameters were similar to maximal diameters.

After superfusion with NNA, significant and similar A3 constriction was observed in the three groups (fig. 2). Superfusion with mefenamic acid induced significant constriction only in groups T and E. This constriction was significantly greater in group E compared with group T ($P<0.001$). No significant A3 constriction was observed after superfusion with Krebs solution alone.

Discussion

The main result of this study was that diaphragmatic arteriolar diameters in anaesthetized rats were affected by the anaesthetic agent used. Indeed, A2 and A3 diameters in rats anaesthetized with etomidate were significantly greater than those in animals anaesthetized with propofol or thiopental. This effect of etomidate was associated with more significant release of vasodilator prostaglandins compared with that during propofol and thiopental anaesthesia.

The experimental model used in this study allowed *in vivo* observation of rat diaphragmatic microcirculation and the diaphragm itself was totally intact. However, the experimental design did not allow comparison of vessel diameters before and after induction of anaesthesia with etomidate, propofol or thiopental. Furthermore, it did not allow evaluation of the effect of the solvents of etomidate or propofol. It must be noted also that the model preparation was performed under ether anaesthesia which takes some hours to be eliminated completely.[22] On the other hand, ether uptake is slow, particularly in skeletal muscles. As the time of ether administration in our

Table 3 A3 diameters (mean (SEM)) in the etomidate (E), propofol (P) and thiopental (T) groups Subgroups C, MA and NNA=preparations superfused with Krebs solution alone, or Krebs solution containing mefenamic acid 20 μmol litre^{-1}, respectively. Significantly different from basal diameter (*$P<0.05$, **$P<0.01$); †significantly different from the other groups ($P<0.05$)

	n	Basal diameter	Diameter after inhibitor	Maximal diameter
Group E				
Subgroup C	19	45.6 (2.8)†	44.1 (2.8)†	41 4 (2.9)
Subgroup MA	13	45.8 (4.1)†	33.7 (3.3)†	48.1 (4.1)
Subgroup NLA	13	44.9(3.3)†	34.9 (3.1)	48.3 (4.1)
Group P				
Subgroup C	12	39.3 (4.9)	38.5 (4.7)	45.7 (4.9)**
Subgroup MA	12	42.5 (2.8)	42.6 (2.9)	55.2 (3.5)**
Subgroup NLA	13	36.3 (3.1)	27.5 (1.7)**	58.2 (3.6)**
Group T				
Subgroup C	13	32.2 (2.5)	33.1 (3)	43.5 (3.9)**
Subgroup MA	14	38.4 (2.7)	35.3 (2.3)	51.8 (3)**
Subgroup NLA	12	35.4 (2.7)	28.6 (2.1)**	48.3 (3.2)**

experiments was approximately 30 min, it seems conceivable that ether concentration in the diaphragm was very low. Furthermore, arteriolar diameters were measured 90 min after the end of ether inhalation, probably allowing enough time for elimination of ether from the diaphragm. Thus although we are not certain that there was no ether effect in the diaphragmatic arterioles at the time of evaluation of the effects of i.v. anaesthetics, it seems unlikely that ether played an important role in arteriolar tone.

Arteriolar diameters were compared after administration of the three i.v. anaesthetics, with maximal dilation achieved using a high concentration of adenosine. Adenosine, a powerful vasodilator which is used frequently to standardize arteriolar reactivity,[23] was used to normalize our results.

Depth of anaesthesia, mean arterial pressures and heart rates were stable and similar in the three groups; there was a lack of response of the animals to painful stimuli and blood-gas values were within normal limits at the end of the study. The doses of thiopental and etomidate used in our study were similar to those used by other authors.[4, 24] We used doses of propofol which were higher than those used in humans because it has been demonstrated in rodents that higher doses of propofol are required to maintain anaesthesia.[25, 26]

In our study, assessment of the role of nitric oxide and prostaglandins in the arteriolar responses of the diaphragm to i.v. anaesthetics was performed indirectly using selective inhibitors of both pathways: NNA for nitric oxide and mefenamic acid for prostaglandins. While NNA and mefenamic acid may have exerted their effects on diaphragmatic arterioles via other mechanisms than inhibition of nitric oxide and prostaglandins synthesis, respectively, this is unlikely. First, a large body of evidence has demonstrated that NNA is a potent and specific inhibitor of nitric oxide synthesis[20, 21] in different vascular territories, including the diaphragm.[21, 27] Second, concerning the involvement of prostaglandins, mefenamic acid has been used extensively as a specific inhibitor of prostaglandin synthesis.[9]

In animals anaesthetized with etomidate, basal arteriolar diameter was similar to maximal diameter after application of adenosine. In contrast, diameters were significantly less than maximal values during propofol or thiopental anaesthesia. As maximal diameters caused by adenosine were similar in the three groups of anaesthetics, it is unlikely that this difference was caused by a greater effect of etomidate on diaphragmatic arterioles compared with propofol and thiopental. Furthermore, as there was no difference in arterial pressure, heart rate or acid–base status between the three groups, it is likely that the high vasodilatory capacity of etomidate was related to a direct effect of this agent on diaphragmatic arteriolar tone.

Similar results have been reported in non-respiratory skeletal muscles by Asher and co-workers,[4] using a cremaster preparation. These authors showed that in rats anaesthetized with etomidate, arterioles were dilated near their maximal diameter (sodium nitroprusside-induced). There are few data on propofol. In work carried out in a dorsal skinfold chamber of the hamster, a large bolus dose of propofol (25 mg kg^{-1}) induced relatively modest (13%) dilation of skin arterioles.[15] However, this effect, which is similar to our data, was not compared with other anaesthetics.

As both mefenamic acid and NNA induced A2 and A3 vasoconstriction in the three groups of animals, it may be that both prostaglandins and nitric oxide are involved in maintenance of diaphragmatic arteriolar tone during etomidate, propofol and thiopental anaesthesia. However, mefenamic acid-induced constriction was more significant in group E than in groups P and T, suggesting a predominant role of prostaglandins in animals anaesthetized with etomidate. This result is partially in agreement with data reported in the cremaster muscle by Asher and colleagues.[4] These authors showed that etomidate-induced dilation was mediated exclusively by prostaglandins but not by nitric oxide. The difference concerning the role of nitric oxide could be related to differences in circulatory characteristics between the cremaster and the diaphragm.

Several studies have investigated whether or not nitric oxide is involved in vasodilatation caused by propofol, with contradictory results.[8, 28–31] Prostaglandins were reportedly involved alone or in concert with nitric oxide in propofol-mediated vasodilatation of rat aorta and coronary arteries, respectively.[8, 31] Our data in A2 vessels are agreement with the latter results because the tone of A2 during propofol anaesthesia was mediated by both nitric oxide and prostaglandins. In contrast, the tone of A3 was mediated exclusively by nitric oxide.

The results concerning the role of nitric oxide and prostaglandins in maintenance of diaphragmatic arteriolar diameter under thiopental anaesthesia agree with previous reports in the same experimental preparation[33] and in other skeletal muscles.[11, 13, 14, 19]

The three i.v. anaesthetics evaluated in this study have differences in cellular effects other than release of nitric oxide and prostaglandins. For example, it has been demonstrated that they affect differently intracellular Ca^{2+} or K^{+} metabolism, or both, in myocardial[32, 33] and tracheal smooth muscle cells.[34] Occurrence of such differences in vascular smooth muscle cells could also be a factor in the observed differences in diaphragmatic arteriolar tone between the three anaesthetics regimens.

In summary, in rats anaesthetized with etomidate, diaphragmatic arterioles were more dilated than in those anaesthetized with propofol or thiopental, a phenomenon which was probably a result of predominant release of vasodilator prostaglandins caused by etomidate. This vasodilatory effect of etomidate may have important implications in pathological situations associated with impairment of the diaphragmatic microvasculature, such as in sepsis.[35]

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Primary afferent-evoked release of immunoreactive galanin in the spinal cord of the neuropathic rat

L. A. COLVIN AND A. W. DUGGAN

Summary

We have determined if peripheral nerve stimulation altered the increased spontaneous release of immunoreactive (ir)-galanin that is found in the superficial dorsal horn of the spinal cord of neuropathic rats. Using the antibody microprobe technique to study the localized sites of ir-galanin release *in vivo*, we found that high intensity electrical stimulation of the injured nerve resulted in a further increase in ir-galanin release in the superficial dorsal horn, with no significant persistence of ir-galanin after release. Release of ir-galanin at stimulus strengths sufficient to activate C fibres, in an area of the spinal cord thought to be concerned with nociceptive transmission, indicates a possible role for this peptide in the spinal modulation of pain after peripheral nerve injury. (*Br. J. Anaesth.* 1998; **81**: 436–443).

Keywords: pain, experimental; pain, neuropathic; spinal cord, galanin; model, rat; rat

It is well known in the clinical setting that damage to a peripheral nerve can result in neuropathic pain. The underlying pathophysiology of these chronic pain states is unclear, but animal models are proving useful in helping to understand the peripheral and central changes that occur after nerve injury. In rats, after peripheral nerve injury, there is evidence of altered behavioural responses suggestive of hyperalgesia and allodynia. Electrophysiological changes have been described in the spinal cord, with evidence of increased spontaneous and evoked activity that may underlie these behavioural changes.[1–4] After peripheral nerve injury, marked changes occur in neuropeptide synthesis in dorsal root ganglion cells and in neuropeptide concentrations in the spinal cord.[5–7] Synthesis of galanin, neuropeptide Y and vasoactive intestinal peptide (VIP) are markedly up-regulated, while substance P (which is normally thought to be concerned with nociceptive transmission[8, 9]) is significantly down-regulated, as are calcitonin gene-related peptide (CGRP) and somatostatin.[10, 11] In this investigation, we have studied galanin. There is some evidence from behavioural and electrophysiological studies that galanin acts predominantly as an inhibitory compound after nerve injury, and therefore it may be useful in the treatment of neuropathic pain syndromes.[12]

In the spinal cord of normal rats, high concentrations of galanin have been found in the superficial dorsal horn, with moderate amounts around the central canal, dorsolateral funiculus and ventral horn.[13–15] Although most of this galanin was thought to originate from intrinsic neurones of the spinal cord, a variable amount has been reported to arise from the termination of small primary afferent neurones.[6, 13, 16–19] The distribution of galanin binding sites in the spinal cord correlates well with the distribution of the peptide itself, as high affinity binding has been found in the superficial dorsal horn and around the central canal.[20, 21] Molecular studies of galanin receptors have found at least three subtypes.[22–24] In the superficial dorsal horn, high concentrations of galanin receptor 1 (galR1) have been found, with both galR1 and galR2 being found on small cells of the dorsal root ganglia.[25–27] The close correlation between galanin distribution and its receptors may indicate that its main site of action is close to its site of release, although significant persistence of galanin after its release could result in more widespread effects.

The functional role of primary afferent contained galanin in the normal animal is unclear as innocuous or noxious peripheral stimulation do not result in central release of ir-galanin.[28, 29] After nerve injury, galanin synthesis was significantly increased in small to medium sized cells in the dorsal root ganglia,[5, 30, 31] with a corresponding increase in ir-galanin in the dorsal horn, particularly in laminae I–III.[32, 33]

There are several possible explanations for the increase in ir-galanin concentrations in the spinal cord after nerve injury. It could result from increased synthesis, central transport and release by primary afferent neurones. Alternatively, it could arise from the response of intrinsic neurones to altered input, as either increased synthesis or inhibition of release could lead to an apparent increase in galanin in the dorsal horn. Another possibility is that degradation of ir-galanin is inhibited in the superficial dorsal horn, for example by some of the other substances that appear in the spinal cord after nerve injury. Therefore, it is important to study release, and per-

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sistence after release. Our experiments were carried out to determine what changes occur in the release of ir-galanin in the dorsal horn of rats as a result of peripheral nerve injury. We have shown previously that basal ir-galanin release was increased in the superficial dorsal horn of neuropathic rats on the side of nerve injury.[34] In this study, we have investigated ir-galanin release evoked by stimulation of the peripherally injured nerve.

Materials and methods

ANIMAL PREPARATION

The study was carried out under Home Office Licence No. PPL 60/1146, and the guidelines for the care of experimental animals set out by the International Association for the Study of Pain were followed.[35]

Preparation of neuropathic model

Peripheral neuropathy was induced in 12 male Wistar rats (200–320 g) (Charles River Ltd, UK), as described by Bennett and Xie.[36] In rats anaesthetized with sodium pentobarbitone 40–50 mg kg^{-1} i.p., the sciatic nerve was exposed by an incision at the mid thigh level, four 4/0 chromic gut sutures were placed loosely around it, and then tissue layers closed with 4/0 vicryl, using full aseptic technique. All animals were housed with free access to food and water, under controlled conditions of light and temperature. Regular monitoring of postoperative development of neuropathic pain behaviour was carried out in all animals.

Behavioural assessment

The main aim of behavioural testing was to establish that all rats in which ir-galanin release was studied displayed signs of neuropathic pain. A combination of tests was used, with the rats allowed to acclimatize, unrestrained, on a cage lid. Von Frey nylon filaments (Stoelting, Ill, USA) were used to assess the degree of mechanical allodynia by establishing the lowest threshold to which the animal withdrew its hindpaw. The lowest threshold filament at which paw withdrawal occurred was established. An upper limit of force of 46.54 g was used, as beyond this stiffness the filament lifted the paw from the floor.

Duration of hindpaw withdrawal to pinprick on the plantar surface of each hindpaw was used as a measure of mechanical hyperalgesia, as described by Tal and Bennett.[37] The stimulus was delivered only once to each hindpaw during any test session, and the total number of test sessions was limited. This was done to avoid confounding factors that may arise from repeated noxious stimulation.

Student's paired *t* test was used to compare the differences between hindpaws at each time for both paw withdrawal threshold and duration.

ANTIBODY MICROPROBE TECHNIQUE[38]

Antibody microprobe preparation

Fine glass micropipettes, with a tip diameter of approximately 10 μm, were coated with rabbit anti-rat galanin antiserum (Peninsula, CA, USA). A detailed description of this technique can be found in Duggan.[39] Briefly, the glass micropipettes were heat sealed, incubated in a 10% solution of aminopropyltriethoxysilane (Sigma) in toluene to coat the outer surface of each microprobe with a fine granular siloxane polymer layer, and then protein A (Sigma) was immobilized on the outer surface by glutaraldehyde coupling. Immunoglobulins in galanin antiserum were bound by protein A to coat the outer surface of the microprobes with galanin antibodies. These coated microprobes can bind endogenous galanin, at localized sites of release, that is detected by subsequent inhibition of binding of exogenous radiolabelled ^{125}I-galanin (Peninsula, CA, USA).

In vitro tests

Prior to commencing *in vivo* work, *in vitro* assays were carried out to determine the specificity and sensitivity of the immobilized galanin antibody by measuring the degree of inhibition of ^{125}I-galanin binding by related peptides or varying concentrations of unlabelled galanin. The amino acid sequence of galanin is quite different from that of opioid peptides[40] making cross-reactivity extremely unlikely. For this reason neither *in vitro* testing carried out in our laboratory nor the manufacturer's data studied opioid peptides in relation to galanin antiserum.

Ir-galanin release experiments

At 10–14 days after ligature placement, rats with behavioural evidence of neuropathic pain were used to study ir-galanin release in the lumbar spinal cord. As previous studies[34] have shown no effect of peripheral nerve injury on spontaneous ir-galanin release in the spinal cord contralateral to the side of injury, microprobes inserted into the contralateral side of the cord were used as controls for microprobes inserted ipsilateral to the nerve injury.

In rats anaesthetized with urethane 1.25 g kg^{-1} i.p. with supplements as required, arterial pressure was monitored continuously, humidified supplementary oxygen was given and body temperature maintained at 36–38°C using a thermostatically controlled heating system. In those animals where paralysis was required (during stimulation of C fibres), vecuronium 1 mg kg^{-1} provided neuromuscular block and a Harvard animal ventilator was used to ventilate the lungs at a rate of approximately 80 bpm.

The lumbar spinal segments, L2–6, were exposed and after the dura was removed, sterile, warmed Ringer's solution irrigated continuously the exposed cord. The ligated sciatic nerve was dissected, covered in warmed paraffin oil and mounted on platinum stimulating electrodes, proximal to the injury. The optimal site for microprobe insertion was determined by nerve stimulation at a low intensity, while measuring the resultant field potentials at a variety of rostrocaudal positions on the spinal cord. Microprobes were then inserted into the area where the largest field potential was measured.

Two different stimulus variables were used to study the effects of peripheral stimulation on release of ir-galanin in the spinal cord: (i) stimulation of large myelinated fibres at 2 Hz, 3 × threshold, 0.1 ms

Table 1 Response to Von Frey hairs and pinprick (mean (SEM)). A significant difference between the values for right and left hindpaw withdrawal threshold and duration from day 3 onwards was detected using Student's paired *t* test at each time. This was maintained until the day of the ir-galanin release experiment at 10–14 days after loose nerve ligation. **$P<0.001$ ($n=12$), nd=not done

	Von Frey filament loading threshold to evoke response (g)		Duration of paw withdrawal in response to pinprick (s)	
	Right side (nerve injury)	Left side	Right side (nerve injury)	Left side
Preoperative	47	47	0.5	0.5
Days 3–4	4.64 (0.8)**	47 (2.3)	11 (2.9)**	0.5
Days 6–8	4.16 (0.4) **	47 (3.2)	nd	nd
Days 10–14 (experiment day)	2.35 (0.2)**	47(2.3)	25 (2.32)**	0.5

pulse duration; and (ii) additional stimulation of small myelinated and unmyelinated fibres at 2 Hz, 50×threshold, 0.1 ms pulse duration. Electrical stimulation with defined variables was used, as opposed to natural stimuli. It was felt that this more quantitative method of stimulation would allow valid comparison between rats.

Using a micromanipulator, each microprobe was inserted to a depth of 2.25 mm, 500 μm from the midline, into the dorsal spinal cord, thus placing the tip in the lower ventral horn. Microprobes were inserted in both sides of the cord and left in place for 15 min to allow adequate binding of extracellular galanin present in the cord. After removal from the spinal cord, microprobes were washed in cold phosphate-buffered saline containing 0.1% Tween 80 to reduce levels of non-specific binding and then incubated for 24 h at 4°C in a solution of radiolabelled ^{125}I-galanin. After washing, the distal portions of microprobes were placed in an x-ray film cassette with a sheet of monoemulsion film (Kodak NMC) for 8–10 days to produce an individual autoradiographic image of each microprobe. To calibrate microprobe depth accurately within the cord, pontamine sky blue was ejected ionophoretically into the cord at a known depth and the exact position of the dye spot measured in post mortem sections of the spinal cord.

Analysis of microprobes[41]

A computerized image analysis system was used to analyse the autoradiographic images obtained from microprobes inserted into the spinal cord. *In vitro* microprobe images for each experiment were also analysed as controls. Binding of endogenous galanin resulted in deficits in binding of ^{125}I-labelled galanin that were detected as localized decreases in optical density by the analysis system. An Imaging Technology PC vision Plus frame grabber board was used to integrate optical density at 10-μm intervals. For each microprobe, a plot of grey scale (i.e. total optical density) against depth of the probe in the spinal cord was obtained. Thus areas where endogenous galanin had bound to the microprobe were shown by areas of low optical density and a low grey scale value.

The mean values for defined groups of microprobes were plotted as the mean (SEM) of the grey scale values at 30-μm intervals against depth within the spinal cord. Each site on the probe was treated as being independent of other sites and thus comparisons between each site were made. Statistical significance was assigned to each site using the Student's unpaired *t* test, and *t* values obtained were plotted against depth within the spinal cord. $P<0.05$ was taken as statistically significant.

Results

BEHAVIOURAL TESTING

The characteristic changes in gait and hindpaw position were apparent in all animals from day 3 after nerve ligation. A limp was evident and the paw held such that only the medial aspect touched the cage floor when walking. The foot was everted with the toes tightly ventroflexed, and there was evidence of abnormal grooming behaviour. The paw withdrawal threshold to Von Frey hairs and duration of paw withdrawal to pinprick are shown in table 1.

Both tests showed altered behavioural responses to mechanical stimulation on the side of the nerve injury. Thus all animals used in the galanin release experiments had evidence of mechanical allodynia and hyperalgesia on the day of the experiment, combined with characteristic gait changes.

RELEASE STUDIES

In vitro testing

The galanin antibody used was C-terminus directed and showed approximately 40% cross-reactivity with porcine galanin (manufacturer's data and confirmed by *in vitro* testing). Several other peptides that are found in the dorsal horn were studied for cross-reactivity. There was no evidence of cross-reactivity between the galanin antiserum and neuropeptide Y, vasoactive intestinal peptide or substance P. Sensitivity tests found greater than 90% suppression with galanin 10^{-5} mol litre^{-1} and approximately 40% suppression with galanin 10^{-9} mol litre^{-1}, indicating that *in vivo* sensitivity was adequate to detect significant areas of galanin release in the spinal cord.

Microprobes inserted into the spinal cord in the absence of peripheral stimulation

The mean image analyses of microprobes inserted into both sides of the spinal cord in the absence of active peripheral stimulation were studied (fig. 1). These observations were consistent with previous results[34] that showed an increased area of spontaneous ir-galanin release on the side ipsilateral to nerve injury. This peaks in the superficial dorsal horn in the area where small primary afferent neurones normally terminate.

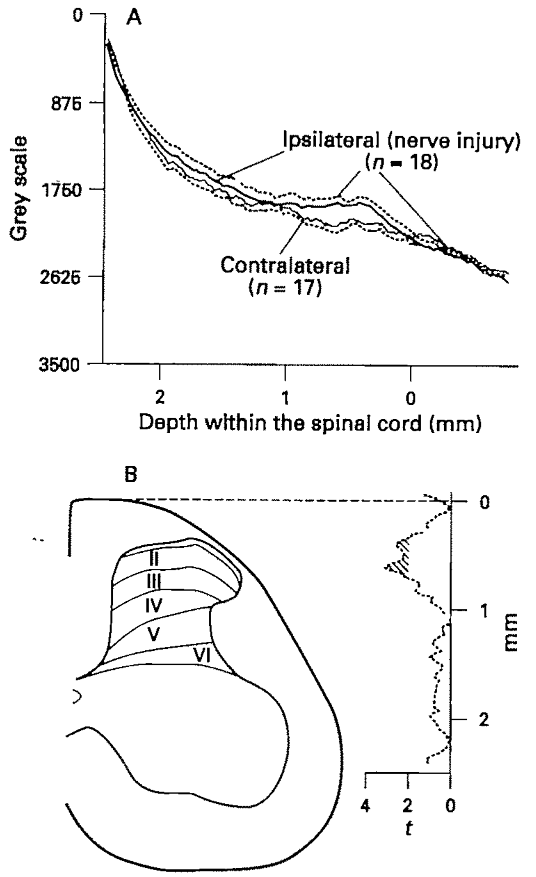

Figure 1 Effects of a peripheral nerve lesion on basal ir-galanin release: comparison of microprobes inserted into the ipsilateral and contralateral side of the spinal cord of neuropathic rats Microprobes were inserted into the spinal cord for 15 min without concurrent peripheral stimulus. A: Mean (SEM, broken lines) image analysis of microprobes inserted into the ipsilateral and contralateral sides of the spinal cord relative to the nerve injury, which is on the right side. The mean image analysis of microprobes inserted on the ipsilateral side is displaced above that of microprobes inserted into the contralateral side, indicating an increase in ir-galanin release under basal conditions. B: Differences between the ipsilateral and contralateral groups of microprobes are shown as t statistics relative to depth in the spinal cord. The diagram of rat lumbar spinal cord is modified from Molander, Xu and Grant.[63] The hatched area shows a significant ($P<0.05$) increase in ir-galanin release on the side of the cord ipsilateral to nerve injury.

Microprobes inserted into the spinal cord during peripheral nerve stimulation

Electrical stimulation of large myelinated fibres. The mean image analysis of microprobes inserted into the right side of the spinal cord (ipsilateral to the nerve injury) before any peripheral stimulus and during 15 min of electrical stimulation is shown in figure 2. A stimulus sufficient to activate large myelinated fibres was used. There was no difference between groups. Thus electrical stimulation of the injured nerve at a stimulus strength sufficient to activate mainly Aß fibres did not alter the release pattern of ir-galanin in the spinal cord from that seen in the basal state.

No change in the pattern of ir-galanin release from that found under basal conditions was seen on the contralateral side of the cord during electrical stimulation of Aß fibres in the injured nerve.

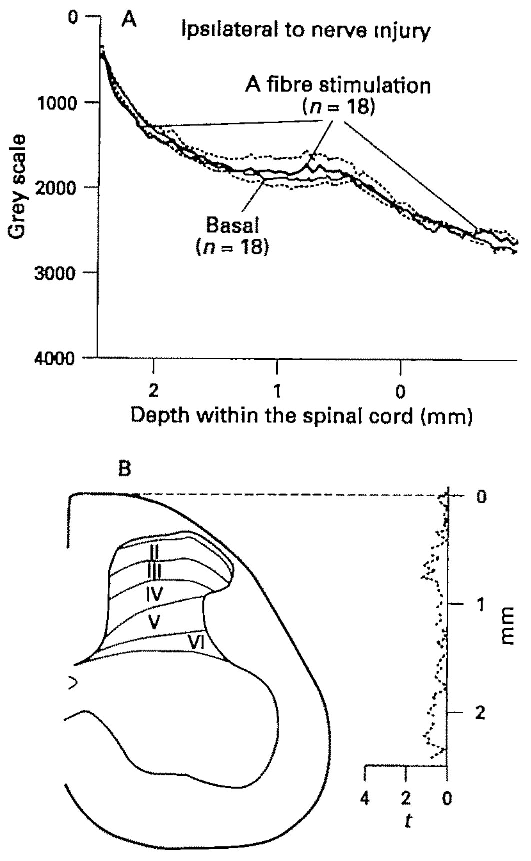

Figure 2 Effects of electrical stimulation of the injured nerve. Microprobes were inserted into the spinal cord during 15 min of peripheral nerve stimulation sufficient to activate large myelinated fibres (2 Hz, 3 × threshold, 0.1 ms pulse duration). A. Mean (SEM, broken lines) image analysis of microprobes inserted into the side of the cord ipsilateral to nerve injury under basal conditions and during peripheral stimulation. B: The t statistic obtained from comparing these two groups at 30-µm intervals along the length of the microprobes is plotted alongside a diagram of the lumbar spinal cord. At no point was there a significant difference between the two groups.

Electrical stimulation of both myelinated and unmyelinated fibres. The mean image analysis of microprobes inserted into the side of the spinal cord ipsilateral to nerve injury without any concurrent peripheral stimulus was compared with that of microprobes inserted during 15 min of high threshold electrical stimulation (fig. 3). Ir-galanin release was increased by this stimulus, with a peak in the superficial dorsal horn. This occurred in a similar area to the increased spontaneous ir-galanin release found in neuropathic rats compared with normal rats. In addition, this increase in ir-galanin release occurred in the area where the small primary afferent fibres terminate, consistent with the idea that the source of the new area of ir-galanin release in neuropathic rats is from small primary afferent fibres.

High threshold peripheral nerve stimulation did not alter the basal pattern of ir-galanin release on the contralateral side of the spinal cord, which was similar to that found in normal rats.

Microprobes inserted into the spinal cord after peripheral stimulation

The mean image analysis of microprobes inserted at 15-min intervals for up to 2 h after peripheral stimulation ceased, was compared with that of microprobes inserted under basal conditions. There were no differences between groups at any point within the spinal

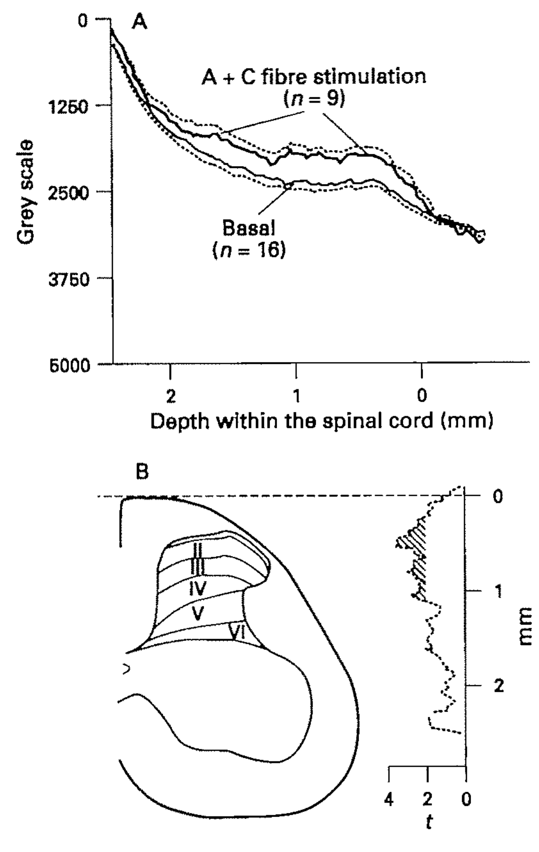

Figure 3 Effects of electrical stimulation of the injured nerve at a stimulus strength sufficient to activate Aβ, Aδ and C fibres on ir-galanin release (2 Hz, 50 T, 0.1 ms). Microprobes were inserted into the side of the spinal cord ipsilateral to nerve injury for 15 min before and during peripheral electrical nerve stimulation. A: mean (SEM, broken lines) image analysis of microprobes inserted into the spinal cord before and during electrical stimulation of the injured nerve. At some points within the cord, the mean image analysis of microprobes inserted during stimulation is displaced above that of microprobes inserted before stimulation. B: Differences between the basal and stimulus groups of microprobes are shown as *t* statistics relative to depth in the spinal cord. The hatched area shows the significantly ($P<0.05$) increased zone of ir-galanin release evoked by high threshold stimulation sufficient to activate both myelinated and unmyelinated fibres.

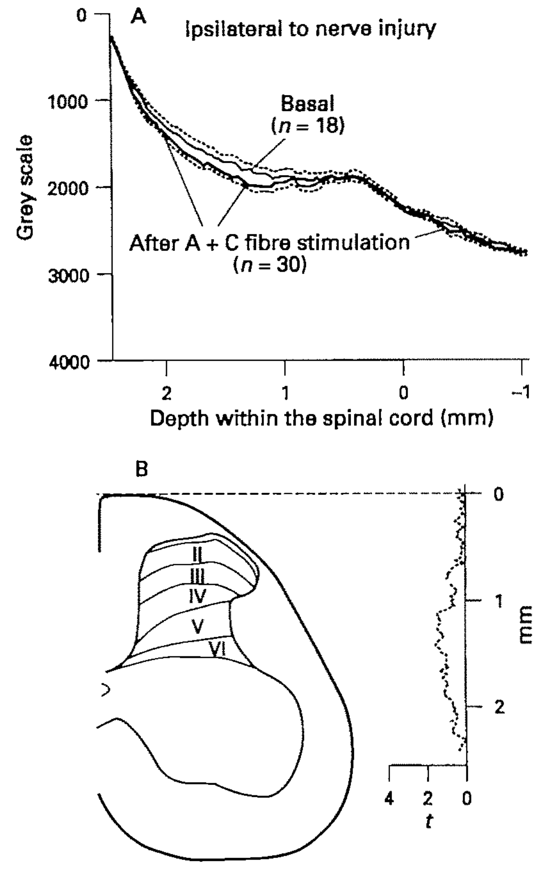

Figure 4 Degree of persistence of ir-galanin after evoked release from high threshold stimulation. Microprobes were inserted into the ipsilateral side of the spinal cord to nerve injury after peripheral stimulation had ceased for up to 2 h afterwards. A: Mean (SEM, broken lines) image analysis of microprobes inserted before high threshold stimulation (2 Hz, 50 T, 0.1 ms) and those inserted during the time from 15 min to 2 h after stimulation had ceased. There was no decrease in optical density of those probes inserted afterwards compared with those inserted under basal conditions. B: Differences between the basal and post-stimulus groups of microprobes are shown as *t* statistics relative to depth in the spinal cord. There was no significant difference between groups, thus providing no evidence for long-term persistence of ir-galanin after C fibre-evoked release.

cord. This indicates that in the time scale studied, there was no evidence for persistence of ir-galanin in the dorsal horn (fig. 4). However, it is possible that released ir-galanin could persist for some minutes, as temporal resolution of the microprobes is limited by the fact that they have to be inserted for 15 min to allow adequate binding. Despite this limitation, our results with ir-galanin are different from those of other peptides studied using the same technique. Neurokinin A and neuropeptide Y, for example, have been shown to persist and spread to sites distant from release, sometimes for hours after stimulated release.[42,43]

Microprobes inserted in the contralateral side of the cord showed no alteration in the pattern of release found under basal conditions during the course of the experiment.

Discussion

The main finding of this study was that ir-galanin release was increased in the superficial dorsal horn after high threshold electrical stimulation of the damaged nerve. This release occurred in the same area of the dorsal horn as increased spontaneous ir-galanin release in neuropathic rats, compared with normal rats. There was no evidence of persistence after evoked release.

SOURCE OF IR-GALANIN

It is important to consider the source of increased ir-galanin release. Possible sources of release include primary afferent neurones, intrinsic neurones of the dorsal horn or descending spinal tracts. Although it has been demonstrated in this study and in others[28] that there is extensive basal release of ir-galanin in normal rats, this is unlikely to be from primary afferent neurones for several reasons. First, there are very low levels of galanin mRNA in the dorsal root ganglia[6,16] and second, peripheral innocuous and noxious stimulation does not alter basal ir-galanin release in the spinal cord of normal rats or cats.[28,29]

The major difference in the neuropathic rats was that stimulation of high threshold neurones (A-delta and C fibres) resulted in a significant increase in ir-galanin in the superficial dorsal horn, unlike that in normal animals.[28,29] Other studies have shown dramatically increased galanin synthesis after nerve injury in small primary afferent cells that normally terminate in the superficial dorsal horn.[5,11] There is also immunohistochemical evidence that the increase in intra-axonal galanin concentrations in the dorsal horn after nerve injury arises from central transport from the cell bodies in the dorsal root ganglia.[44] Our results indicate that evoked release of ir-galanin in the superficial dorsal horn of neuropathic rats is likely to arise from small primary afferent neurones. It is also likely that the significantly increased spontaneous release of ir-galanin previously found in the superficial dorsal horn of neuropathic rats arises from these primary afferent neurones, which have been shown to have increased central transport of ir-galanin after nerve injury.[45]

If the increase in spontaneously released ir-galanin arises from primary afferent neurones, one explanation is that abnormal activity, developing in the primary afferent neurones, provides a stimulus for release. There is increasing evidence that after nerve injury, primary afferent neurones behave abnormally, with generation of spontaneous ectopic activity at the nerve injury site[46,47] and at the cell bodies in the dorsal root ganglia.[48,49] As these afferents are firing spontaneously, it is possible that the spontaneous central release of ir-galanin is caused by these abnormal impulses.

FUNCTIONAL SIGNIFICANCE OF IR-GALANIN RELEASE

The functional significance of galanin and its subsequent effects on neural transmission are not clear, with evidence of both inhibitory[50,51] and excitatory[52,53] effects, including potentiation of the inhibitory effects of morphine.[54] Its presence in the superficial dorsal horn and increased release after nerve injury implies that it may have an important role in the processing of nociceptive information. Our study found that high intensity stimulation of the injured nerve was necessary to evoke ir-galanin release in the spinal cord. Although this is a very potent stimulus, and as such may not represent a "physiological" effect, it helps to support the hypothesis that released ir-galanin arises from small diameter primary afferent neurones. The possible functional effects of released ir-galanin in the spinal cord must be considered. After peripheral nerve injury, behavioural and electrophysiological studies show a greater inhibitory action of galanin. Therefore, it may be more important as an inhibitor of ongoing neuronal activity only after peripheral nerve injury.[12,55] The lack of persistence and spread of released ir-galanin provides a further indication that it acts in or close to its area of release, that is in an area of the dorsal horn thought to be important in the processing of nociceptive inputs.

It must also be considered that galanin may in fact be involved in the development of central sensitization accompanying neuropathic pain. There is a correlation between the rate of ectopic discharge and the degree of spontaneous pain.[56,57] If spontaneously occurring ectopic discharges are causing ir-galanin release, then released galanin could be causing spontaneous pain.

Alternatively, galanin may be not be acting as a neurotransmitter, but may be involved in the reorganizational changes that occur in the dorsal horn after nerve injury.[58] Enhancement of central regeneration of primary afferent neurones has been found after axotomy and nerve crush.[59] Large myelinated fibres have been shown to sprout from deeper in the dorsal horn up to laminae I–II,[60–62] with some evidence of synaptic contacts being formed in these superficial areas. Thus, there is anatomical evidence of altered primary afferent connections in the same area as increased release of ir-galanin. If such stimuli result in ir-galanin release in nerve-injured animals, it almost certainly represents release from primary afferents.

In summary, increased release of ir-galanin in the superficial dorsal horn on the side ipsilateral to a peripheral nerve injury suggests that it plays a greater role in spinal processing in this abnormal state. Spontaneous release of galanin and increased release during stimulation of small diameter primary afferents indicate a role in the processing of nociceptive information. Galanin, or a galanin analogue, may provide a potential new treatment for neuropathic pain syndromes, perhaps by using an endogenous analgesic system similar to that found with opioid peptides. However, further studies are required to elucidate the precise functional role of galanin released into the spinal cord.

Acknowledgements

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Antibacterial activity of lidocaine in mixtures with Diprivan

R. J. Gajraj, M. J. Hodson, J. A. Gillespie, G. N. C. Kenny and N. B. Scott

Summary

We have studied the antibacterial activity of different concentrations of 0.005–2% lidocaine (lignocaine) in mixtures with Diprivan (propofol), against micro-organisms commonly implicated in sepsis as a result of extrinsically contaminated Diprivan. Bacterial colony counts were reduced progressively with increasing concentrations of lidocaine. Bacteriostatic and bactericidal concentrations of lidocaine were 0.2–2%. Lidocaine 2% was not bactericidal for one of the seven organisms tested. By inhibiting bacterial replication, lidocaine, when added to Diprivan to reduce pain on injection, may possibly reduce the harmful consequences if extrinsic contamination occurs. (*Br. J. Anaesth.* 1998; **81**: 444–448).

Keywords: anaesthetics local, lidocaine; anaesthetics i.v., propofol; infection, bacterial; formulations, propofol; formulations, concentration

The lipid-based i.v. drugs Diprivan (propofol)[1 2] and Diazemuls (diazepam)[3] have been shown to support growth of micro-organisms at room temperature. Most other i.v. anaesthetics are not lipid-based, and studies have confirmed that they do not support microbial growth.[4 5]

As a result, there is concern that infusion of Diprivan may contribute to an increased incidence of postoperative infections. Investigators for the Centers for Disease Control (CDC) in the USA found that in some cases of postoperative sepsis, the organism isolated from infected patients was the same as that cultured from the throat or hands of the anaesthetic personnel involved, or from syringes of Diprivan that had been used in these patients.[6 7] Organisms implicated in postoperative sepsis caused by administration of contaminated Diprivan include *Staphylococcus (S.) aureus, Klebsiella pneumoniae, Moraxella (M.) osloensis, Enterobacter agglomerans, Serratia (S.) marcescens* and *Candida albicans.*[6–8]

It is well known that Diprivan is associated with pain on injection.[9 10] Of the many drugs and techniques used to reduce the incidence of pain, only aspirin[11] and local anaesthetics[11–13] have demonstrable antimicrobial activity. The exact mechanism of the antimicrobial action of local anaesthetics is not known, but may be caused by an effect on microbial cell membrane structure or function,[11 14 15] or pH alteration.[16]

The aims of this study were to investigate further the antibacterial activity of lidocaine (lignocaine) in mixtures with Diprivan to determine: the susceptibility of a range of organisms to lidocaine; the concentrations of lidocaine required for bactericidal and bacteriostatic effects; and the antibacterial effects of clinically used concentrations of lidocaine.

Methods

Test mixtures of lidocaine and Diprivan were inoculated with suspensions of organisms, and colonies were counted from samples of the inoculated suspensions after a period of incubation. The organisms used were clinical (hospital) isolates (CI) or standardized typed organisms from the National Collection of Typed Cultures (NCTC) as follows: *Staphylococcus (S.) aureus* (NCTC 6571), *S. epidermidis* (coagulase-negative staphylococcus—NCTC 7944), *Bacillus (B.) subtilis* (NCTC 10452), *Escherichia (E.) coli* (NCTC 10418), *Moraxella (M.) osloensis* (NCTC 10465), *Serratia (S.) marcescens* (CI) and *Burkholderia (B.) cepacia* (NCTC 10743).

The lidocaine–Diprivan test mixtures (5.25 ml) were prepared under aseptic conditions. The quantity of lidocaine in the mixtures ranged from 0.25 ml of 0.1% to 5.25 ml of 2%, producing a range of lidocaine concentrations of 0.005–2%. Diprivan was the diluent used when preparing the lower concentrations of lidocaine. A sample of 1% Diprivan 5.25 ml without lidocaine was also prepared.

Suspensions of the bacteria diluted to a Bacto McFarland Barium Sulfate Standard Number 1 (measured by a Vitek colorimeter), equivalent to approximately 3×10^8 colony forming units (cfu) per millilitre, were prepared. Standardized suspensions containing approximately 10^5 cfu ml^{-1} were made by serial dilution with 0.9% saline. The test mixtures were inoculated with 50-µl samples of the standard suspensions of organisms to produce a final concentration of approximately 10^3 cfu ml^{-1}. These inoculated test mixtures were incubated at 37°C for 24 h. After this initial incubation, 100-µl samples were obtained from each culture and from serial dilutions of each culture, and added to blood agar plates for another 24 h of incubation at 37°C. After this second period of incubation, the resulting colony counts were recorded.

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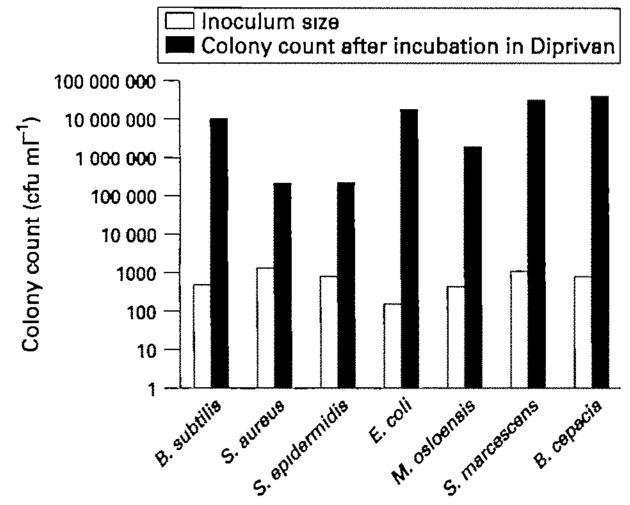

Figure 1 Inoculum sizes (colony counts at 0 h) and colony counts after 24 h of incubation in Diprivan for gram-positive and gram-negative bacteria.

For a more precise measurement of the inoculum size and to verify growth and viability of the organisms, 0.9% saline 5.25 ml was also inoculated with 50 µl of the standard suspensions of each bacterium to produce the same final concentration (10^3 cfu ml^{-1}) as the test mixtures. Samples of 100 µl from this growth control were then added to Columbia blood agar plates and colony counts recorded after incubation for 24 h at 37°C. To verify sterility, samples from the sources of Diprivan, lidocaine and 0.9% saline were also incubated for 24 h at 37°C, and added to blood agar plates for colony counts after another 24 h of incubation at 37°C.

For each organism a bactericidal effect was defined as the killing (or 99.9% elimination) of the initial inoculum, and a bacteriostatic effect as the prevention of growth, that is no significant change in viable count from the initial inoculum.[17] Three replicates were performed with each organism to complete the study.

The Mood Median test (Minitab 10.5 for Windows) was used to compare the colony counts of each organism in each mixture of lidocaine and Diprivan, with $P<0.05$ considered significant.

Results

The final concentrations of the organisms after inoculation in Diprivan–lidocaine mixtures were 160–1350 cfu ml^{-1}. Figure 1 demonstrates the different rates of growth of the various organisms in Diprivan, most notable with *S. aureus*, which was the largest inoculum used yet had the lowest colony counts after 24 h of incubation in Diprivan. Figures 2 and 3 illustrate the colony counts of the gram-positive and gram-negative organisms after 24 h of incubation in the Diprivan–lidocaine mixtures.

With few exceptions, there was a progressive reduction in colony counts of all organisms with increasing concentration of lidocaine (figs 2, 3). Comparing colony counts in the lowest concentration of lidocaine (0.005%) with colony counts in propofol alone, only one organism had significantly lower counts (*E.* coli) while three organisms had significantly higher colony counts. All gram-positive organisms had significantly lower colony counts in lidocaine concentrations of 0.05% or higher, compared with counts in propofol alone (fig. 2). All gram-negative organisms had significantly lower colony counts in lidocaine concentrations of 0.2% or higher, compared with counts in propofol alone (fig. 3).

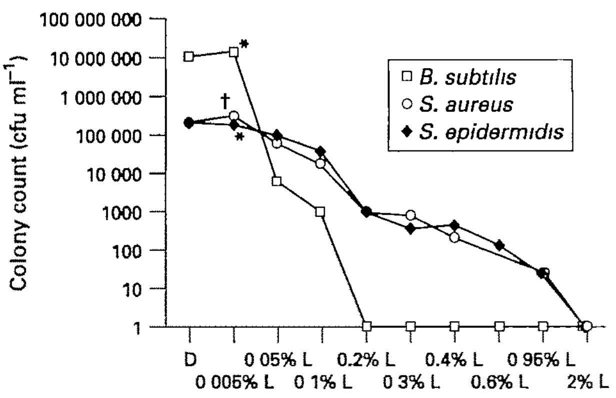

Figure 2 Colony counts for gram-positive bacteria (*B. subtilis*, *S. aureus* and *S. epidermidis*) after 24 h of incubation in Diprivan (D), 2% lidocaine (L) and Diprivan–lidocaine mixtures. †Colony counts higher (Mood Median test, $P<0.05$) than colony counts in Diprivan; *colony counts not significantly lower (Mood Median test, $P<0.05$) than colony counts in Diprivan.

The recommended dose of lidocaine 10 mg in Diprivan 20 ml (producing a concentration of almost 0.05%) produced significantly lower colony counts compared with colony counts in propofol alone, for all except two organisms (table 1; figs 1, 2). Lidocaine 0.1% (20 mg in Diprivan 20 ml) produced significantly lower colony counts for all except one organism.

Figure 4 demonstrates the bacteriostatic and bactericidal concentrations of lidocaine for the organisms tested. Lidocaine 0.2% was bacteriostatic for all of gram-positive organisms. Bacteriostatic concentrations of lidocaine were 0.6–2% for the gram-negative organisms. Bactericidal concentrations were 0.2–2% for gram-positive organisms and 0.95–2% for gram-negative organisms. Bactericidal concentration was not determined for *B. cepacia*, as growth of this organism persisted at the highest concentration (2%) of lidocaine.

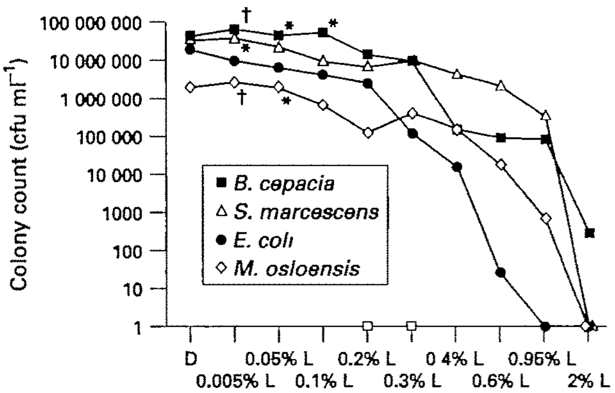

Figure 3 Colony counts of gram-negative bacteria (*B cepacia*, *S. marcescens*, *E. coli* and *M. osloensis*) after 24 h of incubation in Diprivan (D), 2% lidocaine (L) and Diprivan–lidocaine mixtures. †Colony counts higher (Mood Median test, $P<0.05$) than colony counts in Diprivan; *colony counts not significantly lower (Mood Median test, $P<0.05$) than colony counts in Diprivan.

Table 1 Colony counts of gram-positive and gram-negative bacteria after 24 h of incubation in Diprivan and in mixtures of lidocaine (L) and Diprivan. The Mood Median test ($P<0.05$) was used to compare colony counts Lidocaine–Diprivan mixtures with colony counts that were not significantly lower (ns) than the corresponding colony counts in Diprivan alone are indicated

	Colony count in			
Organism	Diprivan	0.05% L	0.1% L	0.2% L
B. subtilis	9 700 000	6 000	947	0
S. aureus	199 333	59 667	17 333	913
S. epidermidis	206 667	95 667	36 567	993
E. coli	15 766 667	5 366 667	3 840 000	2 100 000
M. osloensis	1 733 333	1 633 333 (ns)	593 333	103 000
S. marcescens	30 000 000	20 000 000	8 100 000	5 866 667
B cepacia	36 333 333	37 000 000 (ns)	43 333 333 (ns)	12 200 000

Discussion

Postoperative immunosuppression is well recognized[18–20] and there is also concern that administration of contaminated infusions of Diprivan may contribute to an increased incidence of postoperative infections.

Unfortunately, poor aseptic technique is commonplace among health care workers in the hospital environment,[21 22] and there is poor compliance with data sheet recommendations for the use of Diprivan.[7] This problem is so great that it led the authors of the CDC report[7] and the accompanying editorial[23] to suggest restriction of the use of Diprivan to personnel properly educated in the aseptic techniques of handling the drug. As there is a delay of 8 h or more before organisms begin to multiply rapidly when inoculated into Diprivan, Langevin and colleagues[24] disputed the conclusions of the CDC report[6] that simple bacterial replication in contaminated Diprivan results in postoperative infections. Others have suggested that by careful aseptic handling, it is possible to use the drug in multiple patients or long after opening the ampoule, without significant risk of contamination.[25–27]

The manufacturers recommend the addition of lidocaine 10 mg to Diprivan 20 ml (approximately 0.05% lidocaine) for the relief of pain on injection,[28] as there may be problems of chemical incompatibility with larger doses.[29] Gehan and colleagues suggested that there was no additional improvement in reducing the pain of injection with lidocaine in doses greater than 0.1 mg kg^{-1}.[30] This dose of lidocaine (0.1 mg kg^{-1}) would be achieved with the manufacturer's recommended dose of 10 mg. However, other studies have reported that larger doses of lidocaine are more effective.[31–33] In several hundred anaesthetics at our institution, one of the authors (N. B. S.) has used lidocaine in doses of at least 20 mg in Diprivan 20 ml, and we are unaware of any clinical problems related to this practice. Further, Lilley and colleagues suggested that clinically significant emulsion instability does not occur when lidocaine 20 mg is added to Diprivan 20 ml.[29]

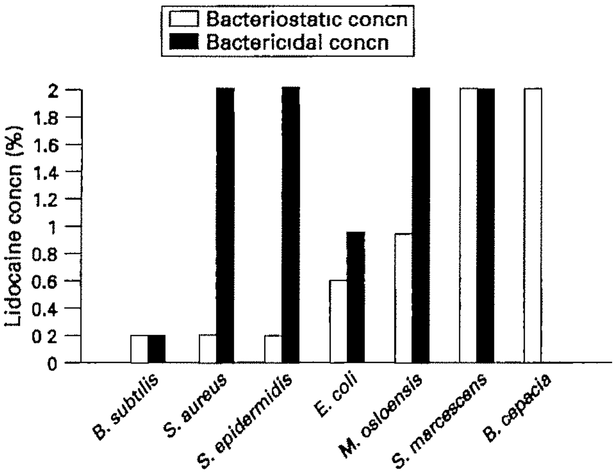

Figure 4 Bacteriostatic and bactericidal concentrations of lidocaine for various gram-positive and gram-negative bacteria The bactericidal concentration for *Burkholderia (B.) cepacia* was not determined.

In our study, the manufacturer's recommended dose of 0.05% lidocaine was not bacteriostatic or bactericidal for any of the organisms tested, although there were significantly reduced colony counts for all gram-positive organisms and two of the gram-negative organisms. Colony counts were reduced further with 0.1% lidocaine (equivalent to lidocaine 20 mg in Diprivan 20 ml), but 0.2% was the lowest concentration of lidocaine with bacteriostatic effects.

The bacteriostatic concentration of lidocaine against *S. aureus* was found to be lower in this study than that reported in some studies[34 35] but higher than in others.[36] The potency of lidocaine against *E. coli* reported in some studies[34 35] was similar to the findings of our study, but greater than in others.[15 37] The potency of lidocaine against *S. marcescens* and *M. osloensis* in one study[35] was greater than that in our study. Fazly Bazaz and Salt concluded that the antibacterial activity of lidocaine was greater against gram-positive than against gram-negative organisms.[15] This is consistent with the findings of our study but contrary to those of Schmidt and Rosenkranz[35] who investigated more than 1200 strains of bacteria and fungi and showed greater antibacterial activity against gram-negative organisms. These inconsistencies may be a result of differences in methodology[34] or pH,[16] presence of preservatives in the local anaesthetic preparations,[34 37] different serotypes of organisms tested,[35] type of growth medium used[38] and size of the initial inoculum.[17]

The size of the initial inoculum is an important factor that influences determination of antimicrobial potency.[17] This should ideally be between $4\text{x}10^5$ and $1\text{x}10^6$ bacteria per sample.[39 40] The use of larger inocula may result in erroneously low antibacterial activity because of the inclusion of spontaneously resistant bacteria,[41] while measurement of ≥99.9% killing for determination of bactericidal concentrations may not be possible with insufficient colonies from small inocula.[39] The inoculum size used in our study was large enough to determine ≥99.9% killing for only two of the organisms tested. Therefore, for the other five organisms, we considered a bactericidal effect to be present when there was complete elimination of bacteria (100% killing). It should be noted that the degree of killing of the initial inoculum considered representative of bactericidal activity has been reported as >98% to 100% by others, although ≥99.9% is used most commonly.[17,42]

Further studies may be useful in determining if other local anaesthetic agents, such as procaine and prilocaine, are more effective than lidocaine as antimicrobial agents at doses that are useful for preventing pain on injection caused by Diprivan. Studies may then be necessary to investigate if the emulsion is stable when the local anaesthetics are mixed with Diprivan at the effective antimicrobial concentrations. Although Weinstein and colleagues[34] found prilocaine and procaine, in common with lidocaine, to be weak antimicrobial agents in comparison with other local anaesthetics, other studies found procaine[35,37] and prilocaine[37] to be more potent than lidocaine.

Strict adherence to the manufacturer's recommendations is the most reliable method for preventing postoperative sepsis caused by administration of contaminated Diprivan. However, by inhibiting the growth of bacteria, lidocaine in the doses used to prevent pain on injection may help to limit the consequences if bacterial contamination of Diprivan occurs.

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REVIEW ARTICLE

Postoperative cognitive deficit in the elderly surgical patient

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Postoperative confusion is frequent in elderly patients, particularly after major emergency surgery. Berggren and colleagues[6] described confusion in 44% of elderly patients after surgical fixation of a fractured neck of femur. Changes in anxiety levels, personality and memory impairment may also occur and contribute to morbidity.[7] Longer-term effects may be possible, such as changes in personality, social integration and cognitive powers and skills, which can be described collectively as postoperative cognitive dysfunction (POCD). Over the past 40 yr many studies have been performed to assess the relationship of these features to anaesthesia and surgery. The incidence reported has varied. Despite radical changes in anaesthetic practice with the development of new drugs and monitoring techniques which should have improved safety, the proportion of patients affected remains similar to earliest reports.[12]

Although the incidence appears unchanged, the number of elderly patients has been increasing, and changing expectations, in addition to advanced and more available surgical techniques means that a larger number of elderly patients undergo surgery. Survival of elderly patients after surgery has been documented in a study of the 5-yr survival of 900 postoperative patients.[26] After an initial high mortality, related to the surgical diagnosis and the urgency of surgery, mortality later approached that of an age-matched population, suggesting that age alone should not be a reason not to operate. If long-term survival is not related to surgery, proportionately more procedures will be performed in older subjects, and increasing expectations of the elderly could extend the "demand" into higher age groups. This possible growth in surgical demand makes it important to establish the features, incidence and causes of POCD.

History

In 1955, Bedford[3] reported dementia in old people after operations under general anaesthesia. He concluded that minor degrees of dementia were common and described 18 extreme examples. No controls were available and the anaesthetic records were incomplete. From the notes that were available, several of the patients experienced severe and prolonged hypotension and the outcome was perhaps not surprising. However, the effects were attributed to the anaesthetic drugs with the recommendation that "operations on elderly patients should be confined to unequivocally necessary cases".

This prompted Simpson and colleagues[75] to prospectively survey physical and mental changes occurring after anaesthesia and elective surgery in an unselected group of elderly patients. A total of 741 patients were investigated; 472 had general anaesthesia, 206 had local anaesthesia and 63 were discharged without an anaesthetic or operation. Patients were asked standardized questions on physical activity, mental ability, personality and general social integration, and scored according to a five-point scale. In addition, patients thought to be at highest risk of deterioration were tested by a psychologist. No patient showed gross dementia. Lesser degrees of deterioration occurred in some patients, as measured by a decrease in grades on the scoring system. Patients who were subjected to formal mental testing showed no change in basic mental ability and nearly all survivors showed good reasons for deterioration unrelated to organic cerebral damage or anaesthesia. They concluded that anaesthesia had no effect on physical activity, mental ability or personality and recorded the clinical impression of an overall benefit of elective surgery in old people. Unfortunately, there were flaws in the testing of these patients and at least one of the patients described has clear postoperative cognitive deficit.

Blundell[12] measured psychological changes with daily ratings before and after operation in 86 elderly patients undergoing elective surgery. Fifty-one healthy patients were also given formal mental tests, which were focused on memory and intellectual functioning. These included Raven's progressive matrices, sub-tests from the Wechsler adult intelligence scale, memory tests for current events and past personal events, the peg board test, star test, pathways tests and delayed recognition tests. They were compared with two control groups. The surgical group showed marked deterioration after operation in the arithmetic and memory tests, both immediately and in the long term. These differences were greatest on the tests requiring organization of thought and continued for several weeks. In addition, five patients were confused for more than 1 week, and a few were noted to have an acute abreaction experience although no permanent effects were

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found. This deterioration was believed to be a result of the effects of the anaesthetic drugs on the cerebral cortex which was aggravated in some cases by additional complications, such as fever, or the drugs given to combat it. However, there is no information on the nature of the surgery or anaesthesia, and the second control group were not matched to the surgical patients.

In a Finnish study of morbidity and mortality,[13] 174 patients, aged 70–92 yr, were followed for 4 weeks after surgery. Mortality rate was 11% overall; 6% in elective cases and 33% in emergency surgery. Patients were asked to report on their own mental and physical activity 4 weeks after operation using a postal questionnaire. Twenty-five patients did not return the questionnaire. Dementia occurred in five patients (2%) but in four it was caused by severe primary disease. However, another 8% of patients reported deterioration of physical or mental activity that was not explained by pre-existing disease or surgical complications.

After these early studies and the persisting controversy, interest was renewed with speculation on possible causative mechanisms. The emphasis moved from pure "incidence" reporting to the search for causes and incidence.

Why does POCD occur?

Bedford[5] believed that anaesthetic drugs were the causative agents, and this was obviously supported by Blundell.[12] In the 1960s, the role of anaesthetic drugs in POCD was investigated. These observational studies continued into the 1980s when many studies were performed comparing the difference in POCD in patients having general anaesthesia with those having regional anaesthesia.

Others, from the 1970s onwards, studied the hypothesis that postoperative mental changes were caused by the physiological effects of the anaesthetic, such as hyperventilation, hypotension or hypoxia, alone or in combination. Other hypotheses speculated on the role of catecholamines or cholinergic transmission in the central nervous system. More recently, genetic markers from dementia studies have been investigated for their predictive value as either indicators or causative elements in POCD.

Is POCD caused by general or regional anaesthesia?

A variety of studies (table 1) have examined changes in mental function in patients having either general or regional anaesthesia, and the differences between the techniques. The surgical procedures have varied from minor (cataract surgery[17 49]), to intermediate procedures (transurethral resection of the prostate[2]) and major surgery (total hip replacement[42 43 70] and total knee replacement[62 87]). Other investigators followed more than one type of operation, for example total hip replacement and total knee replacement,[45] hysterectomy, prostatectomy or joint replacement,[36] transurethral resection of the prostate or hysterectomy.[19] The variety in both type and severity of operation may have distorted the results when small numbers of patients were studied. The studies also differed in whether or not they excluded patients with a wide range of medical and surgical conditions that may have influenced outcome, in particular, emergency or urgent patients.

Some workers identified no long-term difference in postoperative mental function between patients receiving general or regional anaesthesia.[2 9 17 36 45 62 70 87] Others noted a transient decline in both groups, which was measured at either 24 h,[45] 4 days,[2 70] 1 week[49] or 1–7 days.[36] These reflect merely the time chosen by the investigators for the first set of follow-up tests.

Many studies have focused on the differences in outcome in groups of patients receiving either general or regional anaesthesia. Studies comparing elective patients include those of Jones and colleagues,[45] Riis and colleagues[70] and Campbell and colleagues.[17] In a study of functional and cognitive competence after anaesthesia for total hip replacement or total knee replacement,[45] tests of cognitive function showed no change in either the general anaesthetic or regional group. The general anaesthetic group showed a decrease in choice reaction time compared with the regional group (i.e. psychomotor speed had improved), but there was no explanation for this. Subjective complaints of dysfunction of attention, memory, psychomotor coordination and orientation were assessed with a cognitive difficulties scale. Twelve patients in the general anaesthetic group and 11 in the regional group thought that their memory had deteriorated over the 3-month period, but this was not supported by formal psychometric testing.

Riis and colleagues[70] included a combined general and regional anaesthetic group in addition to the two other groups, to test the hypothesis that mental changes may be caused by increased metabolic demands induced by the endocrine–metabolic response to surgery. Patients having regional anaesthesia only, avoid this response and general anaesthesia (the two postulated causative factors in this study) and discrimination of a possible causative factor is not possible. Increases in plasma cortisol and glucose concentrations were inhibited in the two groups receiving extradural anaesthesia. The group receiving extradural anaesthesia alone showed a similar decline on testing as the other groups, and the cause of the decline was thought to be a factor other than the general anaesthetic or stress response. However, other differences were present in this study. Arterial pressure was lower during operation than before induction of anaesthesia in all groups and the decrease differed significantly between groups, being least in the general anaesthetic group. This raised the possibility that hypotension may be involved, and this was also raised in the study by Campbell and colleagues.[17]

Campbell and colleagues[17] showed a decrease in performance in tests of verbal recall, verbal learning, psychomotor speed and tactile naming at 24 h. Although the decrease in the general anaesthetic group was greater, this was not statistically significant. Recovery was apparent 2 weeks after operation, with possible further improvement at 3 months. The Felix Post Unit questionnaire, a test of orientation and memory used to detect postoperative confusional states, showed no significant changes between groups at any time. Nineteen percent of patients in the general anaesthetic group experienced at least one episode of desaturation (less than 91%) in the peroperative period compared with no patients in the local anaesthetic group. Eighteen of the nineteen episodes lasted less than 1 min. (In one extreme case, Sp_{O_2} decreased to 65% and remained less than 80% for 14 min, despite re-intubation and IPPV with 100% oxygen.) Heart rate and arterial pressure in the local anaesthetic group were stable compared with the general anaesthetic group, in whom there were marked changes. Systolic arterial pressure decreased by more than 30% of pre-induction values in 61% of patients. Patients who experienced hypoxia or hypotension showed no gross changes in psychometric performance, and there was no evidence of long-term POCD in either group. Similar studies by Nielson and colleagues[62] and Bigler and colleagues[9] did not identify differences caused by the anaesthetic technique.

A study by Williams-Russo and colleagues[87] of 262 patients undergoing total knee replacement differed from the other studies in that a minimum clinically important difference (CID) in score for each test was defined, using a Delphic panel to reach consensus before the start of the study. A comprehensive battery of 10 neuropsychological tests was devised to test linguistic, psychomotor/attention and memory domains. CID scores at 6 months were compared with baseline and a score of –1, 0 or +1 given depending on whether the observed change was worse, the same or improved. An overall score was then calculated by combining CID scores and a patient was defined as having long-term cognitive deficit if the total score was –3 or less. Unlike many of the earlier studies,[17 42 70] patients with co-morbidity, such as diabetes or previous myocardial infarction, were not excluded from this study nor were patients with psychiatric illness (excluded in[2 9 36 49 62 70]). When cognitive outcome was analysed as a within-patient change, there was no significant difference between the two anaesthetic groups from before operation to 1 week or before operation to 6 months after operation. Similarly, there was no significant difference between the two groups in the percentage of patients with a decline in score on any of the 10 neuropsychological tests at either 1 week or 6 months. The generalized pattern was a decline at 1 week followed by an improvement or return to baseline at 6 months on most tests. The memory tests were found to be the most sensitive to early and late dysfunction. The incidence of delirium was 11% and not significantly different between groups. Long-term cognitive deterioration occurred in three of the 24 delirious patients (12.5%) compared with nine (4.5%) of 198 non-delirious patients, a finding that was not significant. Six percent of patients in the extradural group and 4% in the general anaesthetic group experienced overall long-term cognitive deficit (P=0.50). Increasing age was a predictor of poorer outcome on the digit span and digit symbol test but did not predict overall long-term deficit. There was no interaction between increasing age and type of anaesthesia. Preoperative depression or IQ scores were not found to be predictors of long-term outcome. It was not known if the 5% of patients showing deterioration over the 6 months of the study was in excess of what would be expected in a population not undergoing anaesthesia or surgery. However, epidemiological data from a French study[22] described an incidence of 3% for newly diagnosed dementia in a population of 2726 non-demented elderly over a 3-yr period. Hence the changes after surgery are far more frequent than one would expect naturally.

Two-thirds of the 12 patients who experienced long-term deficits showed signs of deterioration at 1 week, suggesting that long-term effects may be related to perioperative factors. Alternatively, these patients were perhaps at an advanced stage of their natural ageing process which was decompensated and revealed by anaesthesia and surgery. After recovery from the operative insult they continued to age normally and then revealed signs of deterioration at 6 months. In other words, anaesthesia may reveal and hence predict deterioration rather than cause it.

Hole, Terjesen and Breivik[42] were the only group to show a marked decline in the mental function of patients having general anaesthesia compared with those having spinal anaesthesia. Mental function in 60 patients having total knee replacement was assessed before and after operation by an interview with an unblinded investigator. Only major and obvious changes were recorded, such as amnesia for personal details or lack of orientation. In most cases this was confirmed by relatives. Between 4 and 10 months after operation, patients were sent a written questionnaire asking about mental changes noted by the patient or relatives. Daily activity samples revealed significant postoperative hypoxaemia on days 1 and 3 in the general anaesthetic group compared with the regional group. Mental changes were found in eight of the 31 patients after general anaesthetic and in one of the 29 patients after regional anaesthesia. In one patient in each group this was attributed to the central anticholinergic syndrome and resolved after physostigmine. Of the seven remaining patients with mental changes in the general anaesthetic group, three had persistent mental deterioration. One of these died on day 9 and the others were discharged after 14 days. In the follow-up questionnaire of the six remaining patients, who were initially judged to have had mental changes, only two thought their mental function had returned to normal. One patient had complete dementia. The reasons for these mental changes were unclear but it was noted that the seven patients developing mental changes immediately after operation had a greater decrease in Pa_{CO_2} compared with the rest of the group (11.6 to 9.2 kPa). Although arterial pressure during surgery was significantly lower in the regional group compared with the general anaesthetic group, it was concluded that regional anaesthesia was preferable and should be offered whenever possible. Equal numbers of patients in each group (eight) who did not demonstrate mental changes immediately after operation subsequently complained of them on the follow-up questionnaire. These were judged to be slight and not seriously affecting their quality of life.

With the possible exception of this article, no other studies support an adverse effect related to anaesthetic technique or provide evidence against general anaesthesia. However, these articles suggest that other factors may be responsible, such as drug effects, hypoxia or hypotension.

Does anaesthesia *per se* cause POCD?

Subtle changes in mental function after operation occur in patients of all ages.[20 76 78] Smith and colleagues[78] demonstrated postoperative memory deficit

Key to tables

Tests used in cognitive battery

1. Trail making A
2. Trail making B
3. Symbol digit modality
4. Digit span forwards
5. Digit span backwards
6. Selective reminding
7. Visual gestalts learning
8. Visual gestalts recall
9. Picture recognition learning
10. Picture recognition recall
11. WAIS block design
12. Sorting test (willanger)
13 Reaction time
14. Tapping
15. Card sorting
16. Immediate free recall
17. Delayed free recall
18. Delayed recognition
19. Paired associate learning
20. Addition
21. Stroop colour word interference
22. Story recall
23. Visual memory tests
24. Object learning test
25. Digit copying test (DCT)
26. Controlled oral word association test
27. Finger oscillation test
28. Two point discrimination test
29. Hand preference
30. Verbal recall—Rivermead behavioural memory test (PRT)
31. Verbal learning—Fuld object memory test (FOMTL)
32. Tactile naming (FOMTN)
33. Symbol cancellation
34. Boston naming test
35. Digit symbol from WAIS
36 Benton visual retention
37. Benton visual recognition
38. Mattis Kovner verbal recall
39. Mattis Kovner verbal recognition

Drugs used for premedication, sedation or reversal

Mo = morphine
P = pethidine
O = omnopon
A = atropine
H = hyoscine
Pr = promethazine
L = lorazepam
D = diazepam
Dr = droperidol
F = fentanyl
DIH = dihydrobenzperidol
N = neostigmine
G = glycopyrrolate
M = midazolam

Abbreviations for test

AMT = Abbreviated mental test
WMS = Wechsler memory scale
WMS-R = Wechsler memory scale—revised
MMS = Mini-mental state
GEMS = Geriatric mental status examination
VAS = Anxiety visual analogue scale
WAIS = Wechsler adult intelligence scale
WAIS-R = Wechsler adult intelligence scale—revised
SCL-90 = Assessment of psychological symptoms
CAPE = Clifton assessment procedure for the elderly

Other abbreviations

Time = Time testing carried out:
P = preoperative
d = day
wk = week
m = month
Sed = sedation
F = female
Arrows
↑ Increase
→ No change
↓ Decrease

Table 1 Studies of general anaesthesia compared with regional anaesthesia

Study	*n*	Op.	Age (yr) (mean)	Premed.	Sed.	Tests	Time	Results	Deterioration occurs	Diff. Bet. Grps.	Long-term Change
Hole 1980[42]	60	THR	56–84 (71)	Mo+H or A	D	Interview	P,1,3,7,12d 4–10 m	↓ Mental function 7/31 GA grp No change epi grp Equal nos C/O long-term change both grps	Yes	Yes	Slight both grps
Kaarhunen 1982[49]	60F	CAT	>65	A+P	F and D	6 Subtests WMS 4 Luria memory tests Finger tapping	P,1 wk	↓ in WMS + Luria tests at 1 week only stat. significant between grps on Luria tests	Yes	Yes	Not tested
Riis 1983[70]	30	THR	>60	P+Pr		Interview Battery 1–12 Tests 1–5, 19	P,3m P,2,4,7d	↓ Learning retention scores day 2, normal day 7 ↓ tests 1–5 day 2, normal day 4	Yes	No	No
Bigler 1985[9]	40	Acute Hip	>60 (78.9)	P	D prn	Abbreviated mental test	P,1wk,3m	↑ AMT both grps at 1 wk	No	No	No

(*Continued*)

Chung 1987[19]	44	TURP Pelvic fl.rp.	60–93 (72)	None	Dr/F Anx pts only	MMS GEMS VAS	P,6h,1,3,5d,1m P,1m P,1d	↓	MMS in GA grp at 6 h on tests of recall, attention + calculation By day 5 no difference to preop.	Yes	Yes	No
Hughes 1988[43]	30	THR	50–80	T	M	Recall and recognition	P,1,2d,1wk	 ↓	No change recall Repeat recall and repeat recognition Spinal grp worse at 24 h At 1 wk ns diff.	Yes	Yes	Not tested
Ghoneim 1988[36]	105	Hys/ prost/(61) joint	25–86	D	M+/–F	Sickness impact profile, SCL90 Metamemory questionnaire Mental status questionnaire Battery 3,5,13–21,33 Health index Patients self-rated health	P,1–7d,3m	↓	Paired associate learning and general slight decline postop. marked improvement at 3m	Slight	No	No
Asbjørn 1989[2]	40	TURP	60–80 (68.8)	D	F/DIH	Short-term, long-term, verbal and visual memory Battery 4,16,19,22,23	P,4d,3w	→ ↓ ↓	verbal memory excluding Paired associate learning day 4 Visual memory and delayed visual recall	Yes	No	No
Jones 1990[45]	146	THR/ TKR	>60	D (GA grp)	M	Choice reaction time Critical flicker fusion threshold (both Leeds psychomotor) Tests 24,25 Functional life scale Cognitive difficulties scale	P,3m	→ ↑	Most tests cognitive function Functional competence scores but ns Improvement in score for recognition and response component of reaction time in GA grp No change regional grp Equal nos each grp C/O being worse not confirmed by testing	No	No	No
Nielsen 1990[62]	60	TKR	60–86 (70)	D/L (20 %)	D/L	WAIS-R (Satz–Mogel short form) WMS-R Sickness impact profile Tests 1,2,26,27,28,29	P,3m	↑ ↑	In full IQ scale and SIP score in verbal/visual memory, delayed recall and attention/concentration both grps, no difference between groups	No	No	No
Campbell 1993[17]	169	CAT	65–98	O+H or T prn to GA pts	none	Tests 4,5,25,30–32 Felix post unit questionnaire Holbrook activity index	P,24h,2w,3m	↓ ↓ ↑	At 24 h in verbal recall, verbal learning psychomotor speed and tactile naming recovery by 2 w and further improvement by 3 m At 24h greater with GA grp but ns HAI at 3 m.FPU no diff. between grps	ns	No	No
Williams-Russo 1996[87]	262	TKR	>40 (69)	None	M+F	Battery to test Linguistic domain 26,34 Psychomotor/attention domain 1,2,4,5,35 memory domain 36–39	P,1w,6m	 ↓ ↑	Generalized decline at 1w followed by a return to baseline or improvement by 6 m In 3 of the 4 tests of memory 36,38,39 and 1 test of attention 35 at 1 wk At 6 m on 1,2,4,5,26,34–36 No difference between grps Overall 5% showed a long-term clinically significant deterioration	Yes	No	Yes

regardless of age when patients were tested on the second day after surgery, and elderly patients also had problems with orientation and concentration (table 2). A positive correlation was found between postoperative deficit and poor preoperative cognitive function. The relationship between duration of anaesthesia and postoperative deficit was unexpected in that larger deficits were associated with surgery of shorter duration.

Smith and colleagues[76] studied choice reaction times in 112 patients after transurethral procedures at 1, 2 and 3 days after operation; 26 orthopaedic patients, studied at least 12 days after operation were used as controls. An increase in variability in reaction time at 24 h was shown in the study patients but not in controls. Risk factors were a reduced CAPE score before operation, extent of surgery, postoperative pain and postoperative sedative drugs, but age, duration of anaesthesia, minimum arterial pressure, minimum and maximum perioperative P_{CO_2} values, postoperative pyrexia and poor sleep were not contributing factors. Chung and colleagues[20] who studied only 40 patients undergoing cholecystectomy, found no age-related difference apart from performance on the trail making test, which was noted only on the first day after operation.

Tzabar, Asbury and Millar[82] studied 54 patients undergoing day-case anaesthesia for a variety of surgical procedures. Patients were asked to complete the cognitive failures questionnaire (CFQ) for the 3 days before and after operation to provide a subjective assessment of cognitive function. The CFQ consists of 25 questions relating to lapses or mistakes that commonly occur in everyday life. They were compared with 30 patients having local anaesthesia. They reported significantly more cognitive failures in the general anaesthetic group after compared with before operation, and also in the general anaesthetic group compared with the local anaesthetic group. Unfortunately, this study has serious flaws; patients could not be randomized between local and general anaesthesia because of the different surgical procedures. The general anaesthetic group were significantly younger, included more females and had a higher drop out rate, with only 68% returning the second questionnaires. This highly selected group formed the 54 general anaesthetic patients.

Specific anaesthetic/operative techniques causing POCD

POCD IN CARDIAC SURGERY

Cognitive decline is well documented after cardiac surgery (table 3). The extent depends on the time of measurement and the cognitive functions studied. These complications are usually attributed to the adverse effects of cardiopulmonary bypass on the brain. The proposed causes are legion,[18 32 39 68 84] and include preoperative cerebral dysfunction, limited autoregulatory capacity, hypothermia, intraoperative hypotension, loss of pulsatile flow, macro- or micro-embolization of air, or particulate matter or cellular aggregates which may compromise cerebral perfusion. Combinations of these causes may also be harmful; Newman and colleagues[61] reported that the combination of hypotension (mean arterial

Table 2 Studies of general anaesthesia and POCD

Study	*n*	Op.	Age (yr)	Tests	Time	Premed.	Reversal	Control	Results	Effects Exist
Smith 1986[78]	85	Ortho./ Gynae./ General	4 grps M/F and young (50) or old (69)	Orientation—17 questions Concentration—months of the year backwards Visual memory–object learning test	P,2d	A (all pts)	A+N	None	↓ Memory all ages ↓ Orientation and concentration in eldery patients ↑ Impairment preop. leads to greater deficit postop. ↓ Length of procedure = greater deficit postop.	Yes
Chung 1990[20]	40	Cholecystectomy	25–83 2 grps <60(39.7) >60(67)	MMS Tests 1–5 VAS	P,1,2,3,4,30d P,4d	Pr+P (anx pts)	A+N or G+N	None	↓ Digit symbol test day 1 all patients ↓ Trail making test day 1 older pts both back to baseline day 2 → Digit span test or MMS	Yes
Smith 1991[76]	112	Transurethral procedure	48–88 (70)	CAPE preop. Choice reaction time (CRT)	P,1,2,3d	T (all pts)	Variable	26 ortho pts 10 other	↑ Variability in CRT at 24 h not in control ortho pts	Yes
Tzabar 1996[82]	54	Various surg GA	19–60(34)	Cognitive failures questionnaire	P,3d	—	—	LA grp	GA grp significantly more cognitive failures for 3 days postop. compared with 3 days preop. LA grp showed no significant change GA grp significantly more failures than LA grp postop.	Yes
	30	Various surg LA	22–70(48.7)							

Table 3 Studies of POCD and cardiac anaesthesia

Study	*n*	Surgery	Age (yr) mean	Tests	Time	Follow-up rate	Results short-term	Results Long-term
Savageau 1982[73]	245	Cardiac-CABG 75% Valve 14% Combination 11%	25–69 (54.7) — —	Visual reproduction (WMS) Tests 1+2 Logical memory (WMS)	P,9d,6m P,6m	83%	28% decrease on at least 1 test day 9 By 6m more than 80% of these pts normal range	24% of pts impaired at 6m % pts showing decrease on tests = 17% on 1 test, 6% on 2 tests and 1% on 3 tests
Shaw 1987[74]	312 50 20	Cardiac-CABG Control surg Control non-surg.	33–70 (53.4) 41–68 (57.4) 31–61 (46)	Tests 2,11 7 subtests WMS WAIS vocab sub test	P,7d /discharge	96%	↑ Neuro and neuropyschological complications cardiac grp compred with surg. grp but complications exist both grps	Not tested
Townes 1989[81]	90 47	Cardiac-CABG 72% intracardiac 28% Control non-surg.	(?–?) (59) — (?–?) (59)	Shipley Institute of living scale WAIS digit symbol from the Halstead-Reitan neuropsychological battery: Trail making Finger oscillation Sensory perceptual examination Aphasia screening test from the repeatable cognitive–perceptual-motor battery: Peg board Visual search Digit vigilance tasks Selective reminding test WMS—Logical passages and visual designs Hamilton depression scale ratings the subjects subjective anxiety rating	P,8d,7m	87%	↓ On all tests surg,grp compared to controls day 8 ↑ Levels of anxiety and depression surg. grp day 8	General improvement in surg. grp on higher functions 31% showed a decline at 7 m and included a group who were impaired preop. and remained so 11% showed a decline on at least half of the tests
McKhann 1997[53]	172	Cardiac-CABG	41–86 (63)	CES-D depression score Written alphabet test Rey auditory verbal learning tests 1–8 Rey complex figure copy and immediate and delayed recall Grooved pegboard and tests 3–5,21,34	P,1m,1yr	73%	At 1 month ↓ Verbal memory and language domain 30% pts ↓ Visual memory, psychomotor and motor speed in less than 9% of pts ↓ In attention domain 13% of pts ↓ Visuoconstruction 24% of patients ↓ Executive function 6% of pts	At 1 yr Improved most pts Small no. remain impaired 13% remain impaired 33% impaired 11% impaired

pressure <50 mm Hg) and rapid rewarming contributed to cognitive deficit in elderly patients. Detailed study of these reports may provide an insight into the mechanisms underlying POCD in less challenging surgical and anaesthetic procedures.

Savageau and colleagues[73] assessed neuropsychological dysfunction at 9 days and 6 months after elective cardiac surgery, and 83% of patients completed both tests. They were classified as having significant deterioration if their score on a test was more than 1 SD below their preoperative score. Twenty-eight percent of patients showed deterioration in one or more tests on day 9. At 6 months, 76% of patients showed no significant deterioration on any of the five tests, 17 % showed deterioration on one test and 6% on two tests. The greatest deterioration shown, poor performance on three tests, affected only 1% of patients. Of great interest was the finding that only 5% of patients had deficits at both times. Most deficits identified at 6 months had occurred subsequent to the test on day 9. Factors associated with decreased function at 6 months were total estimated blood loss greater than 3000 ml and the use of propranolol during operation. Greater fatigue and depression after operation were also associated with poorer performance.

In 1987, Shaw and colleagues[74] examined the effects of cardiopulmonary bypass by comparing neurological and neuropsychological complications in 312 patients undergoing coronary artery bypass graft with 50 patients undergoing major surgery for peripheral vascular disease. A battery of 10 tests was used, consisting of eight subtests from the Wechsler memory scale (WMS) and two from the Wechsler adult intelligence scale (WAIS). A second control group of 20 non-surgical patients was included to demonstrate the effects of repeating the tests after an interval of 7 days. Reproducibility of results was confirmed by a high Spearman re-test reliability coefficient. Intellectual deterioration was defined as mild (deterioration on 1–2 tests), moderate (3–4 tests) or severe (5 or more tests). In the cardiac group, 61% developed early neurological abnormalities and 79% developed early neuropsychological abnormalities compared with 18% and 31% in the control group. By the time of discharge, 17% of the cardiac group had neurological disability and 38% had neuropsychological symptoms. Of the patients with neurological complications in the CABG group, 48 had minor disability and four major functional disability compared with none in the surgical control group. Twenty-four percent of patients in the cardiac group showed moderate or severe intellectual deterioration compared with none in the control group. Potential risk factors for cerebrovascular disease were more common in the control group and the different results were attributed to cardiopulmonary bypass.

Townes and colleagues[81] also used a non-surgical control group in a study to elucidate the severity and duration of new organic brain dysfunction after cardiac surgery. A group of 65 patients CABG were compared with 25 patients for intra-cardiac surgery to see if there was a difference in incidence caused by the bypass itself. The community volunteers used for the control group had a higher level of education but otherwise there were no differences. A comprehensive battery of psychometric tests were studied. No significant differences were found between the groups undergoing CABG or intra-cardiac surgery at any time, although there was a discernible difference in 31% of patients in either clinical or test performance. At the 7-month follow-up, there was no significant difference between the surgical and control groups for any test except that the surgical group were still rated as more depressed. Patients who started with a poor performance on clinical rating remained so, and eight other patients showed a decline on clinical rating. Increased age was the only significant difference in the impaired group.

Although the level of depression before operation had an impact on tasks such as problem solving and the overall degree of impairment, it did not account for it fully. Depression alone accounted for differences in aphasia and overall impairment at the 7-month follow-up. Membrane oxygenators, arterial filters or pulsatile flow which can improve cognitive outcome were not used. The decrease in cognitive function before discharge may also be attributed to the large doses of long-acting drugs used for anaesthesia and analgesia.

McKhann and colleagues[54] studied the frequency of depression in patients after CABG and its link with cognitive deficit; 176 patients were assessed using the Center for Epidemiological Study of Depression (CES-D) scale and a series of cognitive tests. The CES-D score ranges from 0 to 60 with a score greater than 16 indicating depressed mood. Depression was found to be present in 27% of patients before surgery. In patients depressed before operation, 53% were still depressed at 1 month, and 47% at 1 yr after operation. In the non-depressed group before operation, 13% were depressed at 1 month and 9% at 1 yr. Preoperative depression is thus a good predictor of depression after operation but when cognitive function was compared before operation between the depressed and non-depressed groups, there was a difference in only one area of cognitive function, visuoconstruction. Aspects of cognitive function, such as attention where impairment might be expected in depression, were not affected. This study concluded that postoperative depression (a total incidence of 32% in this study) is linked closely to preoperative depression and is not responsible for the decline in cognitive function demonstrated at 1 month and 1 yr. Patients with prolonged decline and delayed decline had little sign of cognitive impairment at 1 month, suggesting that perioperative hypoxia is an unlikely cause of this decline.

Drug effects

GENERAL ANAESTHETIC DRUGS

Anaesthetic drugs may continue to exert effects on cognitive function at trace concentrations, and this has been investigated over several years. Bruce, Bach and Arbit[14] showed that students exposed to 4 h inhalation of nitrous oxide 500 ppm and halothane 15 ppm in air showed significant decrement in performance on tasks involving auditory and visual signals, memory tests involving digit span, and recall of word pairs. Subjects exposed to nitrous oxide in air showed only a change in the digit span test. Bruce and Bach[15] later reported that inhalation of trace amounts of halothane (1 ppm) and nitrous oxide (50 ppm) produced decrements on tasks of visual perception, immediate memory and a combination of perception, cognition and motor skills. Nitrous oxide alone also produced this effect. Other workers found similar effects[34 35] related to small (20–30%) amounts of nitrous oxide while still others[77] found no effect with either 10% nitrous oxide or halothane 100–150 ppm in air on anaesthetists or students.

PREMEDICATION AND/OR GENERAL ANAESTHESIA

Initial reports of drowsiness and amnesia after general anaesthesia and the possible influence of premedication have led to many studies comparing different drug combinations, and the evaluation of new drugs as they emerge to reduce such side effects. The cognitive impact of premedicant and sedative drugs was investigated by several groups. Feldman[30] compared the effects of four different combinations of premedicant drugs. Patients were assessed using a questionnaire. Amnesia for the preoperative period was significantly more frequent in patients receiving hyoscine, either alone or in combination with papaveretum, compared with patients receiving either pethidine and atropine or promethazine and atropine.

Wetherell[86] showed a significant reduction in digit recall after atropine 2 mg intramuscularly, but the same dose did not show significant effects when given orally. A test of associative memory suggested that atropine impairs memory function by an effect on information storage rather than retrieval.

Karhunen and Jönn[49] used subtests of the Wechsler memory scale (WMS), four memory items according to Luria, and finger tapping, to test elderly women undergoing cataract surgery under either general or regional anaesthesia. Both groups showed a decrease on memory tests at 1 week, but the difference between the general anaesthetic and regional group was only significant for the Luria tests. Patients requiring night sedation were prescribed nitrazepam, and a significant correlation was found between administration of the drug and a decrease in performance on the WMS in all patients, especially in the general anaesthesia group. Hughes, Bowes and Brown[43] tested recall and recognition and found a significant decrease in recognition at 24 h after spinal anaesthesia, which may have been attributable to the use of benzodiazepines for sedation. These studies show how benzodiazepine use can influence outcome.

Gruber and Reed[38] assessed postoperative anterograde amnesia in relation to preoperative medication and/or general anaesthesia. They compared three groups of patients undergoing minor surgery: a general anaesthetic group, spinal group and control group. Both surgical groups were premedicated with atropine 0.4 mg/70 kg, pentobarbital 100 mg/70 kg and pethidine 75 mg/70 kg. General anaesthesia was provided with thiopental, halothane and nitrous oxide. After operation, patients were presented with a question, and auditory, visual, and painful stimuli at set times. Patients receiving general anaesthesia showed a significantly greater degree of postoperative amnesia than patients receiving spinal anaesthesia. Older patients showed poorer performances although this was not statistically significant. They concluded that general anaesthesia, and not the premedicant drugs, was responsible, although other combinations of these drugs may produce more amnesia,[51] as may these drugs if given in higher doses.

Kalman and colleagues[46] compared the effects of propofol and isoflurane anaesthesia (with and without nitrous oxide) on early and late recovery after major abdominal surgery. During the first 2 h, the Steward recovery scale was used, and orientation, comprehension and sedation were assessed. Before and on days 1, 2, 3, 7 and 30 after operation, psychomotor function was tested using simple reaction time and finger tapping. Patients also answered a questionnaire to assess symptoms and mood. Psychomotor function after operation was similar in all three groups and there was significant prolongation of the reaction time and a reduction in finger tapping speed. Patients anaesthetized with isoflurane reported more vegetative symptoms than those anaesthetized with propofol. Patients receiving propofol also reported greater subjective control and were more socially orientated. Addition of nitrous oxide did not change the results.

One of the possible effects of general anaesthetic drugs on cognitive function is an alteration in memory processing. Nordstrom and Sandin[63] demonstrated that patients who were temporarily capable of cognitive action during intermittent propofol anaesthesia had no subsequent explicit recall of intraoperative events. Implicit memory itself appears to be spared during propofol anaesthesia.[21]

Effects of physiological changes during anaesthesia

HYPERVENTILATION

Hyperventilation leading to profound hypocapnia and cerebral vasoconstriction seems a logical cause for cognitive deficits, and this was confirmed by Wollman and Orkin[88] who found that extremes of hypocapnia during anaesthesia were associated with a prolonged reaction time for at least 3–6 days after hyperventilation. This was particularly worrying because hyperventilation was for relatively short periods and in relatively young people. However, other groups[10 59] could identify no significant effect of hyperventilation on cognitive performance.

HYPOTENSION

It was speculated many years ago[3] that POCD may occur as a result of physiological changes during anaesthesia and surgery which adversely affect cerebral perfusion. Intuitively, hypotension may cause cognitive deficits, and such changes have been used by several groups to investigate the role of cerebral perfusion. Unfortunately, the results are less than robust. Gruvstad, Kebbon and Lof[40] found a slightly greater impairment in psychiatric and psychometric tests after hypotensive anaesthesia but considered these changes unimportant in daily living. Eckenhoff and colleagues[25] tested perception and short-term memory, which were considered to be important to everyday life, in a group of younger patients and found no difference in the hypotensive group.

Elderly patients tested 5 days after retropubic prostatectomy showed deterioration on a battery of psychomotor tests in both hypotensive and normotensive groups.[71] All patients received hyoscine premedication and combined spinal–general anaesthesia. In the normotensive group a vasopressor was used to maintain arterial pressure while the second group were allowed to become hypotensive with a mean decrease in arterial pressure of 56% from 154 to 68 mm Hg. There were no differences between the two groups, and by 6 weeks after operation, the tests had returned to baseline. However, one patient from the hypotensive group had a coronary thrombosis and died, and two other patients had adverse reactions, one from each group. Preoperative tests in two patients suggested organic intellectual impairment and one of these (from the normotensive group) was excluded because of difficulty with postoperative testing. This may have biased the results in this small group of 27 patients. Thompson and colleagues[80] examined the effects of hypotension in 30 patients undergoing total hip replacement. Mean arterial pressure was reduced to 50 mm Hg in the two hypotensive groups (10 patients in each group) by the use of either halothane or sodium nitroprusside. In the third group, normotensive arterial pressure was maintained within 20% of baseline. Although no effects were seen on tests of cerebral, hepatic or renal function, or myocardial status at 1–2 days and 7–8 days after operation, one patient in the hypotensive group was disorientated 24 h after operation and nine patients failed to complete tests as a result of pain, immobility or sedation.

The possible effect of prolonged hypotension was not confirmed in these studies, and has not been demonstrated as being significant in the ISCOPD study[58] (see below).

HYPOXIA

Hypoxia is commonly implicated when changes in mental function occur. The pathophysiology is complex and the effects depend on the degree of hypoxia, the time course over which it develops, and whether ischaemia is also present. In mild to moderate hypoxia, the supply of energy to the brain is normal and cerebral ATP concentrations are maintained. In contrast, central neurotransmitter turnover is very sensitive to mild hypoxia. Investigations in which chemical hypoxia and tissue hypoxia were induced in mice showed a decrease in cerebral acetylcholine synthesis. The importance of this in the neurological symptoms of hypoxia was tested by treating mice with an acetylcholinesterase inhibitor. This delayed the time to seizures or death, suggesting that central neurotransmitters, including acetylcholine, may be the cause of impaired brain function in hypoxia.[37] The direct role of hypoxia in POCD has been examined frequently. No difference in cognitive deficit was seen when either air or oxygen was used as the vaporizing gas in elderly patients undergoing prostatectomy.[67] Similarly, when examining the role of pulse oximetry,[57] difference in the rates of postoperative cognitive deficit when pulse oximetry was used (7%) were not found to be significantly different compared with when it was not used (11%). An observer study[56] of hypoxaemia in a PACU demonstrated a lower risk of hypoxaemia in patients who had undergone regional anaesthesia compared with general anaesthesia, but this could not be related to postoperative morbidity.

The pattern of memory deficit after hypoxic ischaemic injury secondary to cardiac arrest has been described and found to have some similarities to the amnesia associated with alcoholic Korsakoff's syndrome, herpes encephalitis and temporal lobe resection.[85] They have the following features in common: (1) intact short-term memory, (2) poor free recall, (3) less depressed recognition ability, (4) some responsiveness to retrieval cues and (5) increased susceptibility to interference. Unlike Korsakoff's syndrome, these patients are orientated and do not confabulate. These clinical features are not commonly seen after operation where disorientation in time and poor short-term memory are the cardinal features.

Studies of patients with severe sleep apnoea syndrome provide further evidence that the role of hypoxia is unlikely to be a direct cause of cognitive impairment. Despite profound and very frequent episodes of arterial oxyhaemoglobin desaturation, occurring every night for years, there has been great difficulty in separating the effects of sleep deprivation from those related to hypoxia.[4 23 28 29 31 83] Treating sleep apnoea with nasal CPAP improves the results of vigilance tests but has little effect on the mild cognitive deficits that have been found. Such studies support the hypothesis that secondary mechanisms, sensitive to hypoxia, are responsible rather than a simple direct action.

Neurotransmitter or neuro-modulation causes

CATECHOLAMINES

In 1975, Drummond[24] reviewed the assessment of postoperative mental function and discussed the possible causes of a decrease in function and the possible role of catecholamines. Wyatt and colleagues[89] studied the effects of altering brain catecholamine concentrations on human sleep. Potent, specific inhibitors of catecholamine synthesis increased total REM sleep with no change in non-REM sleep; serotonin was also found to augment REM sleep. Sung, Frederickson and Holtzman[79] studied the effects of ketamine and thiopental on monoamine concentrations in rat brain. Ketamine caused a slight increase in serotonin and a decrease in norepinephrine concentration. It decreased the apparent synthesis rate of serotonin by 50% while the rate of dopamine synthesis doubled. Thiopental did not affect brain monoamine content but caused a slight decrease in the rate of synthesis of serotonin and a 30% decrease in the rate of synthesis of dopamine. Eger noted that drug induced changes in central catecholamine concentrations affected the potency of anaesthetic agents.[27] It was speculated that the changes in catecholamine concentrations caused by anaesthetic drugs could be directly responsible for the changes in mental function, rather than being the residual effects of the drugs themselves.

The cognitive problems seen with the ß-blocking drugs gave support for this hypothesis, but there is little recent information to confirm a close relationship with circulating or central catecholamines and POCD.

CHOLINERGIC SYSTEM

More recently, the central cholinergic system has been identified as a possible site of action and damage leading to POCD. Smith and colleagues[78] speculated that the memory deficits seen after operation in patients of all ages could result from the anticholinergic effects of atropine used as premedication and also for reversal of residual block. This is supported by the fact that patients with pre-existing cognitive impairment and Parkinson's disease are susceptible to deterioration when prescribed anticholinergic agents.

Delirium is another strong predictor of postoperative cognitive deficit, and could be related to disordered central cholinergic pathways. Knill, Novick and Skinner[50] studied 61 elderly patients undergoing elective abdominal or orthopaedic surgery under general or local anaesthesia, and compared cognitive outcome in patients developing idiopathic postoperative delirium (IPD) with those who did not. IPD developed in 20% of patients, and three of the 12 patients with IPD had significant reductions in mini-mental state (MMS) scores at both times, reflecting performance deficits in two or more functions, compared with only one of the 49 patients without IPD (P=0.009). Knill, Novick and Skinner concluded that IPD was associated with persistent cognitive deficit in some elderly patients. It is not clear if persistent cognitive decline results from delirium itself, if they both result from a separate pathology or an intraoperative event, or if IPD indicates reduced cholinergic reserves.

There is further convincing evidence in geriatric research that confirms that dementia is caused by failure of cortical cholinergic arousal mechanisms.[5 8 11 33 52 72] Markers for the genetic component of this process have been tentatively identified—the apolipoprotein-E[65] gene system. The E4 gene appears to be a marker of poor outcome while the E2 gene appears to be protective. Unfortunately, this has not provided a robust marker in dementia research.[44 47 66] The potential of this gene system to identify patients at risk during cardiac surgery[18 60] has proved debatable. The use of cholinergic enhancing drugs has equally been unsuccessful in the long term.

CONFOUNDING PROBLEMS

One confounding element common to all of the above studies is the possibility that a learning effect on some cognitive tests has occurred, as has been suggested by some authors.[9 62 70 87] However, this has not been confirmed in all studies, for instance a control group of 50 patients[45] on the waiting list for elective joint replacement showed no change over time with the tests used, and no practice effects. Moller and colleagues[58] used a matched control group to determine performance of their cognitive test battery on repeated tests, and this weighting was then applied to their patient data set. This successfully avoids the concerns of practice and learning of such cognitive tests.

Recent research data

THE ISPOCD 1 MULTICENTRE STUDY

The conflicting evidence presented from previous studies, and the possibility that combinations (such as hypoxia and hypotension) may be important, indicated that a definitive study designed specifically to avoid confounding variables was required. Earlier studies suffered from problems with methodology such as small numbers, lack of controls, insensitive psychometric testing, inclusion of patients with pre-existing disease, different medications and incomplete testing. Such problems cause significant bias. A multicentre study, ISPOCD,[58] was performed in 13 centres in eight countries from November 1994 to May 1996, recruiting 1200 patients aged more than 60 yr, undergoing major abdominal, thoracic (non-cardiac) or orthopaedic surgery. Patients with an MMSE equal to or less than 23, CNS disease or receiving interactive drugs were excluded.

The study tested the hypothesis that prolonged cognitive dysfunction occurred after operation, that age was a risk factor and that the combination of hypoxaemia and hypotension were causative factors. A comprehensive battery of six psychometric tests were selected from 12 tests evaluated initially in 50 elderly patients. The battery takes approximately 45 min to complete. It was applied to 176 British volunteers as a normal control population, and a total of 145 national control subjects, aged more than 60 yr, using the same exclusion criteria and time intervals as in the patient study. The test battery was presented to patients before operation, and at 1 week and 3 months after surgery. Patients also performed an IQ test, the Zung mood test, a self-assessment of cognitive decline from the short cognitive failures questionnaire (CFQ) and an estimate of the activity of daily living (ADL) score before operation. The orientation section of the MMSE was administered daily after operation to screen for confusion and delirium. The test battery and Zung scale were repeated on discharge or day 7, and again at 3 months, in addition to the CFQ and ADL. The learning effect was countered by taking the scores of the control individuals and subtracting from the patient scores. The results confirmed that there was a 25.8% (95% CI 23.1–28.5%) incidence of postoperative cognitive deficit at 7 days, and that this still affected 9.9% (95% CI 8.1–12%) of patients at 3 months. Detailed analysis identified only age as a predictor of deficit, and surprisingly that hypoxia, hypotension, or both, were not. The cognitive changes related to decreases in ADL scores showed that these were clinically important changes and not just subtle psychological variations.

FUTURE RESEARCH

There are some firm indications for the directions further research should follow. It is clear that the most promising area where both causation and perhaps prevention may be possible is the central cholinergic system. While the present genetic markers are less than ideal, others may be found that are more specific. The development of drugs for the treatment of dementia will also offer hope that their prophylactic use during operation can reduce the onset of these cognitive deficits.

Equally, there may be subgroups of the population who have critical cognitive functioning, with little reserve, who are vulnerable to the effects of hypoxia and hypotension. Large studies[58] may overwhelm the association of these features in small subgroups, and certainly at present there remains the need to maintain physiological stability during the operation.

Further work is necessary to identify how long the identified deficits last, whether or not they become modified over time, and the social and economic significance of these deficits. It would be valuable to ascertain if regional anaesthesia for major surgery causes similar problems, although current data would support this. Extension of the study groups to include younger patients and ambulatory elderly patients would inform the planning of surgery more precisely.

Conclusions

There is no debate as to whether or not postoperative cognitive deficit exists. It is common and persistent, and should attract the same interest in further research that a similar 25% incidence would obtain if it were found in a young adult or paediatric group. Collaboration with basic science research in progress in the fields of dementia, and in the neurochemistry of the central cholinergic system, may be fruitful in predicting those elderly patients who are most at risk from POCD, and providing effective therapeutic agents to either prevent or reduce the serious effects of POCD on patients and their families.

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SHORT COMMUNICATIONS

Mivacurium compared with succinylcholine in children with liver disease

D. W. GREEN, M. FISHER AND I. SOCKALINGHAM

Summary

We have compared mivacurium and succinylcholine in 27 paediatric patients with mild (Child's A) to moderate (Child's B) liver disease undergoing oesophagogastroduodenoscopy (OGD) and injection of oesophageal varices, with 10 healthy children receiving mivacurium for ENT procedures. With mivacurium 0.2 mg kg^{-1}, the severity of liver disease did not correlate with duration of block compared with controls (time from bolus to T1 25%, P=0.74; T1 25% to T4:T1 >0.7, P=0.545). However, initial recovery (time to T1 25%, P=0.002) and overall recovery (bolus to T4:T1 >0.7, P=0.004) from mivacurium-induced neuromuscular block correlated inversely with pre-existing concentrations of plasma cholinesterase. Conditions for tracheal intubation at 2 min with mivacurium were comparable with conditions at 1 min with succinylcholine in the liver patients. (*Br. J. Anaesth.* 1998; **81**: 463–465).

Keywords: enzymes, cholinesterase; neuromuscular block, mivacurium; neuromuscular block, succinylcholine; anaesthesia, paediatric; liver, disease

Children with moderate to severe liver disease are at risk of developing portal hypertension and oesophageal varices. To limit and prevent episodes of haematemesis necessitates regular oesophagogastroduodenoscopy (OGD) to monitor progress and, if necessary, inject varices with sclerosant.[1] To facilitate this procedure, general anaesthesia and neuromuscular block are used. As the procedure may only last a few minutes if no varices are found, succinylcholine has been the agent of choice in the absence of a non-depolarizing neuromuscular blocking drug of sufficiently short duration.[2] Mivacurium, a short-acting, non-depolarizing benzylisoquinoline neuromuscular blocking drug, is a potentially useful agent in this context. In particular, it has a higher ED_{95} (0.1 mg kg^{-1}), faster onset, shorter duration of action and more rapid spontaneous recovery in children than in adults.[3] This should make it an ideal agent for this procedure.

However, the short duration of action of mivacurium results primarily from its extensive metabolism by plasma (butyryl- or pseudo-) cholinesterase (PChE). PChE concentrations may be reduced markedly in adults with liver disease and thus interfere with the metabolism of mivacurium: there is a significant negative correlation between recovery variables from mivacurium and PChE activity.[4] The object of this study was to evaluate and compare ease of intubation, effective duration of neuromuscular block and spontaneous recovery after administration of mivacurium or succinylcholine to paediatric patients with liver disease requiring OGD. These variables were equated with the pre-existing clinical severity of the liver disease and the concentration of PChE. A control group of healthy children requiring intubation and neuromuscular block were treated with mivacurium.

Methods and results

After obtaining approval from the Ethics Committee of King's College Hospital, we undertook a prospective, randomized, open, between-group parallel study. Groups A and B comprised 27 children, aged 2–12 yr, suffering from mild or moderate chronic liver disease (Child's A or B, ASA II–III), necessitating OGD and possible injection of varices. Group C comprised 10 children (ASA I), aged 2–12 yr, undergoing grommet insertion. Both operations necessitated tracheal intubation. Patients were allocated to group A (Child's A) or group B (Child's B) according to disease severity using a modified Child's classification in use currently at King's College Hospital.[5] Groups A and B were randomized prospectively to receive succinylcholine or mivacurium in a ratio of 1:1. All patients in the control group C received mivacurium.

Anaesthesia was standardized in all cases. After induction of anaesthesia, an i.v. cannula was inserted and blood obtained for measurement of PChE concentrations and estimation of dibucaine number. Neuromuscular monitoring was then attached (Datex Relaxograph, Datex, Finland) and calibrated. The compound evoked potential of the adductor pollicis muscle was recorded after supramaximal stimulation of the ulnar nerve at a frequency of 2 Hz in a train-of-four mode every 12 s. After a 1-min control period, patients allocated randomly to group mivacurium were given a dose of 0.2 mg kg^{-1} i.v. over 30 s and intubation was attempted 2 min after completion of the bolus dose. Patients in the succinylcholine group received glycopyrrolate 10 μg kg^{-1} i.v. followed 30 s later by succinylcholine 2 mg kg^{-1} over 15 s and

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intubation was attempted 1 min later. Ease of intubation was assessed as follows: grade 1 (excellent), easy passage of the tube without coughing, vocal cords relaxed; grade 2 (good), passage of the tube with slight coughing/bucking, vocal cords relaxed; grade 3 (poor), passage of the tube with moderate coughing/bucking, vocal cords moderately adducted; and grade 4 (not possible), vocal cords tightly adducted.

End-tidal carbon dioxide and isoflurane were maintained at 3.5–4.5% and 0.5–1%, respectively, in all patients.

The following measurements were made from the Datex Relaxograph: percentage block at time of intubation (1 min with succinylcholine, 2 min with mivacurium); time from completion of administration of the first bolus dose to 25% recovery of T1; time from 25% recovery of T1 to T4:T1 >0.7 (mivacurium only); and time from administration of the bolus dose to T4:T1 >0.7 (mivacurium only). Neuromuscular function was allowed to recover spontaneously in all patients.

All statistical significance tests were two-sided at the 5% level.

Mean age of the patients was 6.4 (range of 2.2–11) yr. There were no significant differences between groups.

Mean concentrations of PChE (normal range 600–1400 iu litre^{-1}, measured using the method of Kalow and Lindsay[6]) in the three groups were: group A, 700 (SD 170), (range 282–991) iu litre^{-1}; group B, 510 (201), (239–991) iu litre^{-1}; and group C, 932 (165), (734–1224) iu litre^{-1}. Mean PChE concentration was significantly greater ($P<0.05$) in healthy children compared with the liver patients.

Grade of intubation with succinylcholine at 1 min and mivacurium at 2 min showed no significant differences in the specified comparisons. In the 16 patients who received succinylcholine, intubation conditions were 14 grade 1, one grade 2 and one grade 3. In the 21 patients who received mivacurium, intubation conditions were 20 grade 1 and one grade 4.

There were no significant differences between the controls (group C) and the mivacurium-treated patients (groups A and B) for: time (min:s) from bolus to T1 25% (group C, 10:48 (SD 2:54) *vs* group A, 9:50 (2:58) and group B, 12:44 (2:46) ($P=0.74$)) and T1 25% to T4:T1 >0.7 (group C, 5:59 (1:22) *vs* group A, 6:28 (1:42) and group B, 8:18 (2:57) ($P=0.545$)). Thus there was no evidence of prolongation in the overall recovery of mivacurium between Child's A and B and the control group. Recovery was faster in both groups with succinylcholine: time (min:s) from bolus to T1 25% (group A, 7:48 (3:45) and group B, 8:31 (1:51) ($P=0.007$)) and time from T1 25% to T4/T1 >0.7 (group A, 2:02 (3:00) and group B, 1:11 (1:11) ($P=<0.001$)).

Correlations between recovery variables and baseline PChE concentrations were calculated for mivacurium patients. Figure 1 shows a scatterplot of the predicted time, expressed as natural log, from administration of the bolus dose to 25% recovery of T1 and PChE concentrations in the mivacurium patients. The estimated correlation coefficient of −0.81 ($P=0.002$) indicates that high baseline concentrations of PChE were associated with shorter recovery times. Similarly, time from bolus administration to T4:T1>0.7 and PChE concentrations produced a correlation coefficient of −0.80 ($P=0.004$). In contrast, the estimated correlation coefficients of −0.14 ($P=0.725$) and −0.21 ($P=0.61$) indicate no evidence of an association between PChE concentrations and time from 25% recovery to 75% recovery of T1 or time from 25% recovery to T4:T1>0.7.

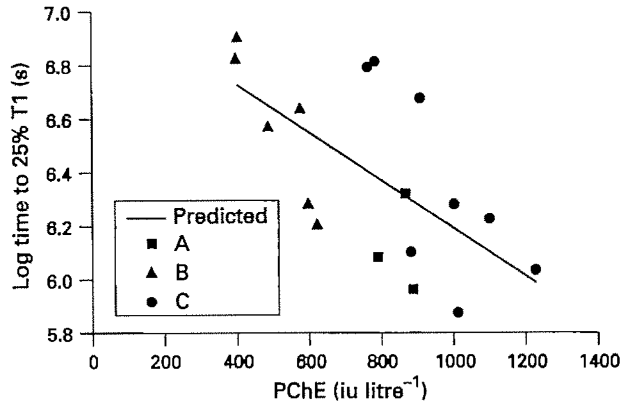

Figure 1 Plasma cholinesterase activity (PChE) *vs* natural log of time from administration of the bolus dose to 25% recovery of T1 in group A (Child's group A patients), group B (Child's group B patients) and group C (healthy patients). Predicted time is expressed as natural log from bolus dose to 25% recovery of T1 in the mivacurium patients. Stratified correlation coefficient = −0.81, 95% confidence interval −0.94, −0.35, $P=0.002$.

Comment

In our study of 10 healthy adult patients and 25 patients with cirrhosis of the liver who received a bolus dose of mivacurium 0.15 mg kg^{-1}, we found that patients with hepatic cirrhosis may be sensitive to mivacurium, which could be explained, at least in part, by lower PChE activity.[7]

Our study has shown that in children with liver disease undergoing OGD and possible injection of oesophageal varices, duration and recovery from neuromuscular block with mivacurium 0.2 mg kg^{-1} did not correlate with the pre-existing clinical severity of liver disease (Child's A or B). However, recovery significantly correlated inversely with pre-existing concentrations of PChE. Conditions for tracheal intubation at 2 min with mivacurium were comparable with conditions at 1 min with succinylcholine. This implies that mivacurium is a suitable neuromuscular blocking drug in this group of patients which may be used instead of succinylcholine.

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Atropine premedication and the cardiovascular response to electroconvulsive therapy

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Summary

A report by the Royal College of Psychiatrists recommended avoiding atropine premedication during electroconvulsive therapy (ECT). We have examined the cardiovascular effects of ECT with or without atropine premedication. Consenting patients (n=30) were allocated randomly before their third ECT session to receive atropine or no premedication. The rate pressure product (RPP) was recorded before anaesthesia, before ECT stimulus and at 1-min intervals thereafter for 5 min. Patients who did not receive atropine had significantly lower RPP values after all stimulus recordings. Administration of atropine or not explained 32% of the variance of summated RPP after the stimulus. There was no clinically significant bradyarrhythmia in those who did not receive atropine. Our findings support the recommendation of the Royal College of Psychiatrists. The study suggests that when threshold determination is not needed, avoiding atropine effectively contains potentially harmful cardiovascular responses. (*Br. J. Anaesth.* 1998; **81**: 466–467).

Keywords: premedication, atropine; brain, electroconvulsive therapy; cardiovascular system, responses

Cardiovascular changes occur consistently during electroconvulsive therapy (ECT). Acute increases, albeit transient, occur in heart rate and arterial pressure, and hence rate pressure product (RPP), an index of myocardial oxygen consumption.[1] During modified ECT, a reduction in arterial oxygen saturation can occur even after adequate ventilation. The increase in RPP during ECT can create an imbalance between myocardial oxygen supply and demand. Treatment variables, such as ECT laterality (bilateral *vs* unilateral) and anaesthetic agent (thiopental *vs* methohexital) do not differentially reduce heart rate or arterial pressure after ECT.[2] Stimulus laterality may not offer a means of controlling cardiovascular responses during ECT. Other strategies aimed at reduction of heart rate and arterial pressure include pretreatment with nifedipine, labetolol or esmolol. Although these methods are effective in the attenuation of the cardiovascular response, they are usually reserved for patients with compromised cardiac function.

Atropine premedication produces anticholinergic-mediated tachycardia. This effect, in addition to the intense sympathetic response after the ECT stimulus, can potentially contribute to greater myocardial work load. In contemporary ECT practice, subconvulsive stimuli used in stimulus titration, increases the risk of bradyarrhythmias.[3] However, there may be advantages in withholding atropine in subsequent ECT sessions where subconvulsive stimulation is absent. There are reports that atropine could compromise cardiac stability[4] and for this reason current guidelines from the Royal College of Psychiatry recommend avoiding atropine during ECT.[5] We have examined the effect of atropine on RPP in a randomized, controlled design during the third ECT session.

Methods and results

We studied 30 consecutive right-handed patients (mean age 27.3 (range 15–50) yr;15 males) referred for ECT after obtaining written informed consent. Patients continued to receive concurrent psychotropic drugs before the ECT session; these were neuroleptics (n=23), tricyclic antidepressants (n=5) and trihexyphenedyl (n=6). All patients were ASA grade I. During the third ECT session, patients were allocated randomly to one of two equal groups to receive atropine premedication or no atropine.

Modification of the ECT procedure was achieved using atropine 0.15 μg kg^{-1} (if given), thiopental 3 mg kg^{-1} and succinylcholine 1 mg kg^{-1} i.v., in that order. The psychiatrist and anaesthetist were blinded to the treatment groups. Intermittent positive pressure ventilation with 100% oxygen was provided until resumption of spontaneous and regular breathing. ECT was administered using a constant current bidirectional brief pulse ECT device (mean stimulus dose 154 (SD 50.2) mC). The choice of ECT stimulus laterality was determined by the referring psychiatrist. In the third ECT session, patients received either threshold bilateral (n=18) or suprathreshold (twice the threshold) right unilateral (n=12) ECT; all developed a seizure in response to the first stimulus in the session. Seizure duration was monitored using an EEG from F_3 and F_4 sites referenced to ipsilateral mastoids (mean duration 65.5 (SD 38.1) s). Cardiovascular monitoring was performed using an

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automated cardiac monitor (pulse oximetry, non-invasive arterial pressure (AP), ECG lead II tracing and heart rate). The product of heart rate and corresponding systolic AP was RPP. Cardiovascular recordings were made before anaesthesia (just before administration of the premedication), before stimulus application (45 s after injecting the premedication and just before stimulus application) and five times at 1-min intervals after the stimulus.

For statistical analysis we used the software package SPSS (v. 6.0). RPP values in the two groups were compared using two-way repeated measures analysis of variance (RMANOVA). Summated RPP (arithmetic sum of RPP at the five recordings after the stimulus) was subjected to linear regression using age, sex, atropine status, stimulus laterality, stimulus dose, EEG seizure duration and pre-anaesthesia RPP as the independent variables. Significance (a) was fixed at 5% or lower.

The two groups were comparable in stimulus dose and laterality, in addition to seizure duration. Significant increases in RPP occurred during the procedure (occasion effect: F=9.7; df=168, 6; P< 0.001). The increases in RPP were smaller in the group that did not receive atropine (group effect: F=10.5; df=28, 1; P=0.003) (fig. 1).

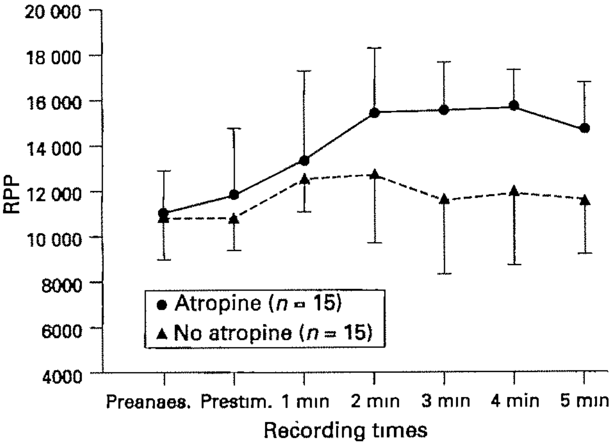

Figure 1 Effect of electroconvulsive therapy (ECT) on the product of heart rate and systolic arterial pressure (RPP) in patients who received atropine 0.15 μg kg^{-1} and in those who did not. Recordings were made before administration of atropine (Preanaes.), after induction of anaesthesia but before ECT stimulus (Prestim.), and at 1-min intervals after the stimulus for 5 min.

In the multivariate, stepwise, linear regression model, only atropine premedication emerged as a significant predictor (B=14343; t=3.6; P=0.001) accounting for 32% of the variance (r^2) in the summated RPP after the stimulus.

There were no clinically significant cardiac arrhythmias in either group.

Comment

Routine atropine premedication during ECT has been recommended by Abrams[6] who argued that the risk–benefit analysis favours the use of anticholinergic agents. This is contrary to the the Royal College of Psychiatry's recommendation of avoiding atropine premedication during ECT.[5]

We found that mean RPP was attenuated when atropine premedication was withheld. Linear regression analysis showed that atropine alone substantially contributed to RPP after the stimulus. Withholding atropine did not affect seizure duration or produce bradyarrhythmia. An advantage of our study is that automated cardiac monitoring eliminated rater bias.

Sustained increases in RPP in patients given atropine increase myocardial workload and oxygen demand. Withholding atropine demonstrably controlled RPP without compromising cardiac stability. Therefore, routine administration of atropine in ECT sessions not involving threshold determinations in ASA I patients is not recommended. However, caution is advised in extrapolating our results to older patients and those who are not ASA I.

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CASE REPORTS

Adrenal failure in the critically ill

M. DUGGAN, I. BROWNE AND C. FLYNN

Summary

Three critically ill patients suffered multiple organ failure secondary to sepsis. Despite adequate supportive therapy and appropriate antibiotic cover, they failed to improve and required inappropriate inotrope support. They had not been treated with steroids or other drugs known to suppress adrenal function. Adrenal insufficiency was suspected. A random cortisol concentration and a short synacthen test demonstrated concentrations below the range expected in all three cases. High-dose steroid therapy was commenced with marked improvement in the short-term. However, in each case sepsis eventually caused death. (*Br. J. Anaesth.* 1998; **81**: 468–470).

Keywords: intensive care; kidney, failure, hormones, adrenal

In the past, steroids were used in the treatment of many disorders commonly seen in the intensive care unit (ICU). The inflammatory nature of these disorders and the known anti-inflammatory effect of steroids made these drugs an obvious therapeutic choice in critically ill patients. However, the results of the use of steroids in humans have been disappointing. As a result of these studies, corticosteroids are not recommended for the management of severe sepsis, including septic shock and adult respiratory distress syndrome.[1]

However, it is important to remember that a small number of patients develop adrenal insufficiency in severe illness and require steroid replacement. Adrenal failure in the critically ill may be difficult to recognize as the syndrome is often masked by other causes of hypotension and organ failure.[2] Weakness, fatigue, weight loss and hypotension, the traditional symptoms of adrenal insufficiency, occur in most ICU patients and are therefore of little value in making the diagnosis. The metabolic upset that occurs in critically ill patients with multiple organ dysfunction also renders the classical electrolyte abnormalities seen in adrenal failure meaningless. A less recognized indicator of adrenal insufficiency is resistance to beta-adrenoceptor stimulation.[3]

We present three cases of adrenal insufficiency. In each case suspicion of adrenal failure was raised only when an inappropriate amount of inotropic support was required.

Case reports

PATIENT NO. 1

A 75-yr-old male presented to a district hospital with abdominal pain and distension. His past medical history included a diagnosis of Felty's syndrome and chronic renal impairment. Felty's syndrome consists of rheumatoid arthritis, splenomegaly and neutropenia, leading to repeated infections and weight loss. The patient had never been treated with steroids. He was transferred to our tertiary referral centre for further management. Two days of conservative management resulted in no improvement. Laparotomy was performed and splenectomy was required for a ruptured spleen. His initial postoperative course was uneventful. However, he deteriorated on day 6 with generalized sepsis requiring respiratory and haemodynamic support. Repeat laparotomy was performed; a necrotic appendix was removed and a transverse loop colostomy made. His sepsis resolved and he was weaned from inotropes. Two days later he again required increasing amounts of epinephrine to a maximum dose of 100 $\mu g\ kg^{-1}\ min^{-1}$, despite no definite focus of sepsis being identified and remaining apyrexial.

The possibility of adrenal insufficiency was raised and a short synacthen test was performed. It revealed a baseline serum cortisol concentration of 0.01 $\mu mol\ litre^{-1}$, increasing to 0.16 $\mu mol\ litre^{-1}$ after administration of ACTH. These concentrations were well below those expected in a critically ill patient and steroids were commenced (hydrocortisone 100 mg qds). Within hours, inotropic requirements were reduced markedly and subsequently discontinued. However, his condition deteriorated again over the next few days and the patient died of massive colonic haemorrhage.

PATIENT NO. 2

A 61-yr-old woman with a 12-yr history of polymyositis was admitted for elective plasma exchange therapy to alleviate worsening weakness of her neck, arms and muscles of swallowing. She had been receiving maintenance therapy of cyclophosphamide 50 mg daily (an alkylating agent) and had never been treated with steroids.

Her hospital stay was complicated by chest infection and the organism *Klebsiella pneumoniae* was isolated. Initial management with antibiotics and CPAP via a face mask was unsuccessful and she required tracheal intubation and artificial ventilation. Inotropic therapy was commenced and titrated to maintain an adequate mean arterial pressure as

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evidence of septic shock developed. Her requirements for epinephrine reached 80 μg kg^{-1} min^{-1}. She progressively developed multiple organ failure, including renal failure, requiring continuous veno-venous haemodiafiltration (CVVHDF). Within 72 h the septic shock had improved but she still required epinephrine 10 μg kg^{-1} min^{-1} to maintain adequate mean arterial pressure.

Given the inotrope requirements, the possibility of adrenal insufficiency was raised. A short synacthen test was performed which revealed a random cortisol concentration of 0.245 μmol litre^{-1} and a post-synacthen concentration of 0.454 μmol litre^{-1}. This was felt to be an inadequate response for a stressed patient. She was commenced on hydrocortisone 100 mg qds. Within 2 h, her inotropic requirements were reduced to 5 μg kg^{-1} min^{-1}. They were reduced further overnight and discontinued the following day. She continued to improve on maintenance steroid therapy. A further episode of sepsis 2 weeks later was treated unsuccessfully and she died on day 21 of her ICU stay.

PATIENT NO. 3

A 52-yr-old man presented to our accident and emergency department with a 3-day history of progressively worsening respiratory distress associated with mild wheeze, pleuritic pain, haemoptysis and intermittent sweats. He also gave a history of influenza for the preceding 2 weeks. Broad-spectrum antibiotics were commenced to cover a community acquired infection. He was treated with flucloxacillin, cefotaxime, erythromycin and gentamycin. CPAP via a face mask was used to improve gas exchange. He deteriorated and required tracheal intubation, artificial ventilation and inotropic support. Epinephrine was titrated to maintain mean arterial pressure greater than 60 mm Hg. He rapidly developed multiple organ failure and required CVVHDF.

His critical condition was felt to be secondary to septic shock but the possibility of adrenal failure was suggested because of the high requirements for epinephrine (100 μg kg^{-1} min^{-1}). A short synacthen test was performed. The basal cortisol concentration was 0.17 μmol litre^{-1} and post-ACTH 0.18 μmol litre^{-1}. He was commenced on hydrocortisone 100 mg qds. For 72 h the inotropic demand was reduced greatly and the dose of epinephrine was reduced to 20 μg kg^{-1} min^{-1}. Despite maximum cardiovascular and respiratory support he failed to improve. He died on day 21 in the ICU from multiple organ failure.

Discussion

Absolute adrenal insufficiency occurs uncommonly in the general ICU population but in certain subgroups the risk of developing adrenal insufficiency is significant. Several studies have reviewed the incidence of adrenal failure in the critically ill patient. It ranges from 6.25% to 75% depending on the population tested.[4] Patients who are not responding to standard therapy should be suspected of adrenal insufficiency.

In patients with septic shock, serum cortisol concentrations are usually increased compared with those in unstressed, healthy individuals.[5] Cortisol plays an important role in the ability to respond to stress. There is a decreased rate of cortisol clearance from the body and reduced binding of cortisol to transcortin, resulting in an increase in circulating free cortisol concentration in acute illness.[6 7] Thus critically ill patients generally show hypercortisolaemia.[8–11] The benefit of this increase is thought to be maintenance of intravascular volume.

There is a small group of patients in whom adrenal hyporesponsiveness is a feature. The aetiology of this relative insufficiency is complex. "Stressed" adrenal glands are more susceptible to haemorrhage and adrenal vein thrombosis.[12 13] Failure of such patients to respond to therapy such as antibiotics, prompt and aggressive fluid management and, if possible, removal of an infective focus should arouse suspicion of adrenocortical insufficiency.

Because of the extremely wide range of plasma cortisol concentrations seen in ICU patients, caution is needed when applying normal values for plasma cortisol to acutely hospitalized patients. High basal cortisol concentrations in septic shock may still indicate relative adrenal insufficiency. On the basis of a recent study of plasma cortisol concentrations in patients with sepsis or trauma, a plasma cortisol value of more than 0.7 μmol litre^{-1} in a patient requiring intensive care rules out adrenal insufficiency, but a safe lower cut-off value is unknown.[14]

An inadequate response to ACTH may identify patients who would benefit from corticosteroid therapy. A short ACTH stimulation test, known as the synacthen test, using a single i.v. dose of cosyntropin 250 μg is recommended.[15] An adequate response is defined as an increase in plasma cortisol concentration of greater than 0.25 μmol litre^{-1} and a peak concentration of 0.7 μmol litre^{-1}. An inadequate response warrants immediate high dose cortisol therapy. Hydrocortisone 100 mg qds is the recommended dose for pharmacological treatment in these patients.[16 17]

Acknowledgements

M. Duggan and I. Browne wish to dedicate this manuscript to Dr Catherine Flynn who died unexpectedly in December 1997

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British Journal of Anaesthesia 1998; **81**: 471–472

Repeated transient neurological symptoms after spinal anaesthesia with hyperbaric 5% lidocaine

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Summary

We report a case of repeated delayed pain after cystoscopy under spinal lidocaine anaesthesia, which may be caused by transient radicular irritation. The possible aetiology of the symptoms is discussed. (*Br. J. Anaesth.* 1998; **81**: 471–472).

Keywords: anaesthetics local, lidocaine; anaesthetic techniques, subarachnoid; complications, transient radicular irritation

Lidocaine (lignocaine) has been used extensively in spinal anaesthesia since 1949. However, following the description of cauda equina syndrome in 1991 after continuous spinal anaesthesia via microcatheters,[1] lidocaine has been associated with transient neurological symptoms when used as a single injection for spinal anaesthesia. The first cases of transient radicular irritation (TRI) with lidocaine were reported in 1993.[2] We present a case of repeated pain after spinal anaesthesia with lidocaine.

Case report

A 74-yr-old man with a superficial bladder tumour was scheduled for cystoscopy. His past history included transurethral resection of his bladder tumour 3 months earlier under spinal anaesthesia. History, physical examination and laboratory results were otherwise unremarkable. Spinal anaesthesia was performed using a sterile technique in the sitting position with a 24-gauge Sprotte needle (Pajunk, Germany) in the L3–4 interspace using the midline approach. After confirming free flow of clear cerebrospinal fluid, 5% hyperbaric lidocaine 75 mg was injected with no dilution. There was no pain or paraesthesia during insertion of the needle or injection of drug. Analgesia to T10 was achieved with no hypotension, and without the use of vasopressors.

Surgery was performed in the lithotomy position and lasted 30 min. Motor function in the legs returned 110 min after spinal puncture and the patient was moved to the ward with instructions to mobilize 6 h later. The patient had no complaints on the following morning but before discharge he asked if he was going to have the same discomfort he had felt after previous surgery. He explained that on the day after his previous surgery, he felt pain in the hips, buttocks and legs, radiating to the toes, which increased on the second postoperative night (36 h after the procedure). The pain was worse at rest and he thought it was a result of anxiety. He did not recall any weakness, headache or fever. The pain disappeared after 24 h without the use of analgesics.

Review of the past anaesthetic record revealed spinal anaesthesia with a 24-gauge Sprotte needle, 5% hyperbaric lidocaine 75 mg, no hypotension, a 45-min surgical procedure in the lithotomy position, motor function returning 100 min after injection of lidocaine and mobilization 6 h after anaesthesia. We delayed discharge, and that afternoon, 30 h after spinal puncture, the patient complained of similar symptoms. Pain was characterized as dull, involving the hips, buttocks and legs, radiating to the toes. There was no headache, fever, or sensory, motor or muscle tendon reflex abnormalities. There were no signs of bladder or bowel dysfunction. Acetaminophen 500 mg orally every 6 h partially improved his symptoms. The pain never reached the intensity of the first episode and disappeared completely after 18 h. There were no sequelae and the patient was discharged. Interestingly, 6 months later, two 30-min cystoscopy procedures performed under general anaesthesia in the lithotomy position were not associated with these symptoms.

Discussion

We have presented a case of repeated pain associated with the use of spinal lidocaine. The symptoms were similar to those described in the literature but interestingly, the patient did not complain of problems after the previous surgery. The syndrome may have been missed as many patients are discharged before symptoms occur. We believe that it is necessary to ask all patients who have received previous spinal anaesthesia specifically about this complication.

Even though the first description was with 5% hyperbaric lignocaine,[2] TRI has been described with lower concentrations and osmolarities.[3,4] Prospective studies with spinal lidocaine have shown an incidence of TRI of 10–37%.[5-7] Lidocaine can produce rapid neurological damage in animal models with no recovery of normal function.[8] In contrast, in TRI, there is delayed onset associated with complete recovery. Therefore, TRI may not be related to drug

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toxicity (defined as persistent biochemical, functional or structural effects[9]) but to a delayed irritative process of unclear aetiology.

Whether the pain is radicular or myofascial is not clear. Bilateral pain is not typical of a myofascial aetiology, and neither is relief with movement. Although TRI has been described in all positions,[5] its incidence is higher in the lithotomy position, perhaps because of stretching of the lumbosacral nerve with possible compromise of neural perfusion and increased vulnerability to the effects of lidocaine. Another explanation of TRI may be nerve or spinal cord ischaemia, related to lidocaine-induced reduction in nerve blood flow,[10] the position of the patient and concomitant use of non-steroidal anti-inflammatory drugs (NSAID).

In contrast with our case, some patients with TRI present with central pain (burning or electrical quality with hypersensitivity or decreased sensation) which improves with anticonvulsant and antidepressant treatment.[11] The only clinical finding in our patient was the delayed onset after a possible injury.

It is improbable that TRI has been unrecognized for almost 50 yr (after approximately 50 million administrations of spinal lidocaine) and therefore other factors need to be considered.[12] Recent changes in clinical practice that could be associated with an increased incidence of TRI include use of pencil-point needles, early mobilization of patients after spinal anaesthesia and use of NSAID. Pencil-point needles are less traumatic to the dural membrane, but slow injection through a side-port needle directed sacrally can lead to high peak concentrations of injected drug,[13] and its blunt tip might dislodge the arachnoid membrane from the dural sheath producing bleeding (with nerve root irritation).[12] Three prospective studies published to date have been performed with different needles and positions,[5-7] and none has addressed the question of early mobilization or NSAID use.

Regardless of the cause, the clinical course of our patient was similar to that reported previously with lidocaine,[2 7] implying a common mechanism. Additional studies are needed to determine the aetiology of these symptoms.

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CITATION CLASSIC

Commentary

Allen TH, Steven IM. Prolonged endotracheal intubation in infants and children. *British Journal of Anaesthesia* 1965; **37**: 566–573.

Several factors were responsible for the rapid changes in the management of acute respiratory disease in infants and young children in the 1950s and 1960s. These included the establishment of paediatric cardiac surgery which often required postoperative respiratory support and the realization that mechanical ventilators, which had been designed either for operating theatre use or in the management of poliomyelitis, could be helpful in other situations.

The only method of securing the airway in critically ill children at that time was by tracheostomy, and in most centres around the world this carried a high incidence of complications and a high mortality, especially in infants and small children. It was this unacceptable incidence of complications that stimulated Allen and Steven to pioneer the use of prolonged tracheal intubation as an alternative method of airway control outside the neonatal period. The concept was not of course new, as laryngeal intubation using silver or vulcanite tubes had been used in the management of diphtheria since 1887. Resistance to the widespread use of these tubes was probably largely because of the trauma of intubation. Brandstater reported encouraging results in 12 neonates and young children using tracheal tubes made of polyvinyl chloride in 1962 and within a year the Adelaide group had begun to use this technique as an alternative to tracheostomy in the management of croup.

Although some aspects of the care of children who undergo intubation, such as the use of steam tents to provide humidity, seem primitive today, this classic article identified almost all of the important issues in the care of these patients. There is an interesting reference to the value of applying continuous positive airway pressure during induction of anaesthesia to reduce airway obstruction, which is as important today as it was in 1965. The risk of infection was identified and it is a sad fact that anaesthetists have not always given the same degree of attention to aseptic techniques when handling tracheal tubes as recommended by these authors. The incidence of tube blockage serious enough to require a change of tube (two of 61 cases) is as low as that reported 25 years later from a major paediatric intensive care unit with modern humidification equipment.[1] It is also interesting that despite the seemingly primitive method of tube fixation, there is no mention of accidental displacement of any tube, a complication which occurs in 3–4% of cases in most units even today.

The most serious complication of this technique, subglottic stenosis, was described clearly in this article and its relationship to tracheal tube size identified in one case report. This complication was later shown to be avoidable if careful attention was given to tube size by Stocks[2] whose group in Melbourne also published their preliminary results in this journal in 1965.[3]

The authors also draw attention to the distress which basic intensive care techniques, such as tracheal intubation, can cause, particularly to older children, which suggests that this group were not only in the forefront of the technical management of children receiving intensive care but also of the humanitarian approach to their management.

In these days when many people take an almost iconoclastic approach to outcomes, it is worth noting that only one of the 10 deaths reported in this series occurred in a child whose respiratory problems were not secondary to other life-threatening disease or injury. Even this child was a neonate with such major multiple congenital abnormalities that it would have been unlikely to survive even given the benefit of the full range of modern intensive care facilities.

Nasotracheal intubation now has a fundamental place in paediatric intensive care. It is salutary to remember that in the early 1960s, tracheostomy was so well established under the care of the surgeon that it must have taken remarkable courage and persuasion by these two anaesthetists to bring about this radical change in management which spread so rapidly around the world. The introduction of this technique, with the acceptance that responsibility for maintaining the airway and supporting respiration lay with the anaesthetist, was also a major factor in securing the central role of the anaesthetist in paediatric intensive care medicine. It is also interesting to note that Allen and Steven emphasized the importance of co-operation and understanding between members of staff, a philosophy which at least in the UK has allowed the development of an inter-collegiate approach to intensive care medicine in both adults and children.

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PROLONGED ENDOTRACHEAL INTUBATION IN INFANTS AND CHILDREN

BY

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SUMMARY

A series of sixty-one cases of prolonged pernasal intubation in children for conditions which would otherwise need tracheostomy is presented. One serious complication, namely subglottic cicatricial stenosis of the trachea, has occurred and is discussed. There is a definite place for prolonged pernasal intubation in children under 5 years of age as an alternative to tracheostomy. The most important single element in achieving success with this technique is to choose the smallest size tube which gives a quiet (adequate) airway and reasonable access for aspiration of secretions.

The management of acute respiratory disease in infants is a problem in any hands. Tracheostomy, although frequently a lifesaving measure, nevertheless carries a high incidence of complications and a high mortality in infants and small children. Table I summarizes our experience with tracheostomy in this hospital over the 11-year period 1950–60.

TABLE I

Admissions for "croup"*	Tracheostomy	Deaths	Overall mortality	Tracheostomy mortality
1,829	59	18	1%	30%

In other words, during this period, 3 per cent of all admissions for croup* had a tracheostomy and of these cases, 1 in 3 died. Few, if any, of these operations were performed in a theatre by a trained surgeon and none had a general anaesthetic. Of these 18 deaths, 5 patients died during or very shortly after tracheostomy, 7 as a result of pneumothorax following tracheostomy, and 6 from bronchopneumonia or purulent bronchitis. In retrospect, therefore, many of these tracheostomies were carried out too late, and earlier operation might have reduced the mortality figures by about one-third. Earlier operation under endotracheal general anaesthesia might possibly have further reduced the mortality by almost another third.

In the last four years in this hospital, almost all tracheostomies have been done in an operating theatre by a trained surgeon under endotracheal general anaesthesia. The dramatic change that occurs in the patient's condition after intubating and re-establishing a clear airway has to be experienced to be appreciated. Table II shows the figures for the next four years individually for each year.

None of the recorded eight deaths was related in any way to the operation of tracheostomy or its complications. The decrease in numbers during 1963 and 1964 is due to the introduction of prolonged pernasal endotracheal intubation.

In principle, this is not a new technique (Gillespie, 1941; Neffson, 1949; Scholes, 1920), but even in their heyday when laryngeal diphtheria was the main indication for their use, O'Dwyer's tubes (Northrup, 1894; O'Dwyer, 1887, 1894) or modifications thereof made of silver or vulcanite were highly controversial. Nevertheless, it is clear from the literature that prolonged perlaryngeal intubation gave acceptable results in the hands of

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* The term "croup" applies here to those conditions in which obstruction, most commonly due to oedematous narrowing of the upper respiratory tract, has occurred. It is characterized clinically by hoarseness, stridor, and occasionally a harsh metallic cough. It is a common sign in many upper respiratory infections in infants, but becomes of grave significance only when the diagnosis is one of either acute laryngotracheobronchitis or epiglottitis.

TABLE II

	Admissions for "croup"	Tracheostomy	Deaths	Overall mortality
1960/61	231	18	2	1%
1961/62	218	18	6	3%
1962/63	251	12	0	—
1963/64	240	4	0	—
Total (4 years)	940	52	8	0.8%

those who acquired the art of introducing the tubes atraumatically by touch. More recent attempts have been mostly unsuccessful (Sykes, 1960) although with adults isolated cases, often in unusual circumstances, proved more promising (Briggs, 1950; Foregger, 1946; Urry, 1951).

The physical properties of polyvinyl chloride—its malleability and plasticity at body temperatures, coupled with its remarkable biological inertness—make it an almost ideal material for indwelling tubes of many kinds. Using endotracheal tubes of this material, Brandstater (1962) achieved encouraging results in a small series of twelve cases, six of whom were neonates. However, only one of these twelve cases had obstructive laryngotracheitis. During the past two years, therefore, all patients in whom formerly tracheostomy would have been performed have been managed instead with an indwelling pernasal endotracheal tube made of polyvinyl chloride. The purpose of this communication is to review experience of this technique in sixty-one children.

At the point when it was decided that the airway must be secured, the child, if conscious was given an anaesthetic and intubated.

TECHNIQUE

The nature and choice of anaesthetic was decided by the anaesthetist. In most cases, a dangerous degree of upper respiratory obstruction was present. The child was restless, often in spite of previous sedation, and the pulse rate rising. An inhalational induction was the most commonly used approach in these circumstances, using either halothane in oxygen or in 50 per cent nitrous oxide and oxygen with strong assistance to inspiration in order to increase the pressure difference across the obstructed segment of the airway. There was never any need to increase the indicated halothane concentration beyond 2 per cent.

No premedication was given, but a nurse or assistant was detailed specifically to keep a finger on the pulse throughout the entire manoeuvre.

Irregularities of pulse rate, volume, or rhythm gross enough to be picked up by palpation were on no occasion a worry. It was almost always possible to abolish, and always to diminish, rib retraction and other signs of respiratory obstruction with effective and sustained intermittent positive pressure assistance to the respiration. With quiet respiratory effort temporarily re-established direct laryngoscopy was carried out. If this provoked no reaction on the part of the child, a Portex* tube of suitable size was passed through one nostril into the pharynx whence it could often be guided directly through the larynx, assisted, if necessary, with a push by means of Magill forceps. When subglottic oedema was dense the tube often entered the larynx readily, but needed quite a firm push with forceps to get it through the region of oedema. The nasal route was used in all cases. This appeared to cause less disturbance to the patient and in the case of older children ensured that they did not, accidentally or otherwise, bite on the airway.

After intubation the child was "specialled" in a steam tent. The tube was moistened every 15 minutes with normal saline or sterile distilled water and for the first 24 hours tracheobronchial suction was performed half-hourly after the preliminary installation of ¼–1 ml of 5 per cent sodium bicarbonate. The tube was changed only when and if signs of obstruction occurred. This was rare, never due to kinking, and only twice due to accumulation of dried secretions at the tip of the tube. Tracheobronchial suction was carried out regularly but with decreasing frequency as time progressed. Full aseptic precautions with a no-touch technique were maintained. Multiple-hole plastic oxygen catheters, with an end-opening moulded tip, as well as side holes, proved effective and relatively atraumatic suckers. A fine endobronchial suction catheter was occasionally invaluable (Bush, 1963). The size of the catheter was dictated by its efficiency in aspirating the bronchial tree. The finest catheter that resulted in a clinically clear airway was the one of choice.

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* Thin-walled Portex tubes of appropriate size were used. These are made of polyvinyl chloride, and are obtainable from Portland Plastics Ltd., 197 Knightsbridge Road, London, S.W.7.

The pulse and respiration rates were recorded at half-hourly intervals. Fluid balance was kept and charted for at least 24 hours. Vomiting was a not infrequent complication of an indwelling pernasal endotracheal tube. A negative fluid balance over a short period occasionally proved worrying. A sustained drop in urinary output along with other clinical signs of dehydration would have made intravenous therapy mandatory, but did not in fact occur. Antibiotics were given if and as directed by the paediatrician in charge of the case. Culture of the aspirate at the first intubation was useful in this regard. The anaesthetist accepted responsibility for maintaining the airway and supporting respiration. Co-operation and understanding were the keynotes to the management of these cases.

When, on clinical grounds, we felt the tube could be removed, we took it out, usually under general anaesthetic on about the seventh day. The voice was husky and the respiration occasionally croupy for as long as seven days afterwards. The child was left in steam always for 24 hours, and sometimes longer, according to need. If respiratory obstruction recurred, re-intubation was performed.

The clinical grounds referred to above were at first somewhat nebulous and each case was very much one of trial and error. In the latter part of the series, however, three clear-cut criteria emerged which, if all three were present, ensured with some degree of certainty an uneventful extubation. These criteria were:

(*a*) Temperature normal for at least 24 hours, preferably 48–72 hours.

(*b*) Return to normal health as indicated by the child's alertness and interest in his toys, his surroundings, and his food.

(*c*) A loose-fitting tube. Evidence of this was shown by an obvious cough around the tube during aspiration. It was not a common sign, but quite characteristic when present.

On discharge, the child was given an appointment for check laryngoscopy in three months' time.

RESULTS

Table III, and figures 1 and 2 summarize our experience with these cases. It can be seen from the wide variety of conditions for which intubation was undertaken that the only common factor in these patients was the need to secure a clear airway. Figures 1 and 2 emphasize two further facts; these are that some 80 per cent of the patients in the series were intubated for a total period of less than two weeks and that 79 per cent of them were less than 4 years old.

TABLE III

Indication for intubation.

(A) ACUTE UPPER AIRWAY OBSTRUCTION	
Laryngotracheobronchitis	27
Oedema of epiglottis and larynx due to inhalational burn	1
Acute epiglottitis	5
Supraglottic submucous cyst	2
Post-laryngofissure as a temporary dilator	1
Bronchitic element predominating:	
Bronchiolitis and bronchospasm	4
Laryngomalacia	1
Pierre Robin syndrome	2
Total	43
(B) THREATENED OBSTRUCTION AND RESPIRATORY INSUFFICIENCY	
Poisonings—barbiturates, strychnine and organic phosphate	4
Unconsciousness: head injury	4
Unconsciousness from other causes:	
Meningitis, encephalitis, status epilepticus	8
Fulminating staphyloccocal pneumonia	2
Total	18

Altogether there were ten deaths. None of these was related to intubation itself. Nine of them occurred in patients listed in group B of table III. The tenth was a feeble neonate with a severe degree of laryngomalacia along with other troubles, namely spina bifida with meningomyelocele, talipes equinovarus, as well as probable intracranial birth injury. Again, the tube had nothing to do with her ultimate demise. Of the

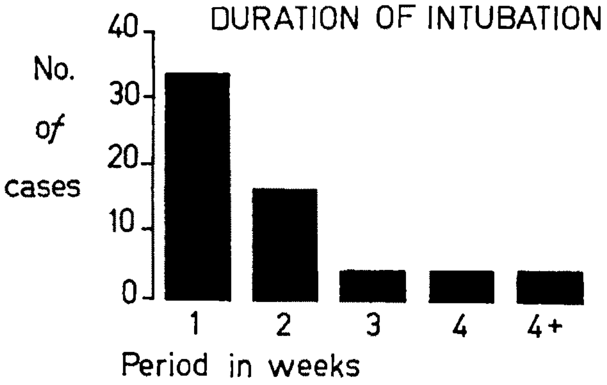

FIG. 1

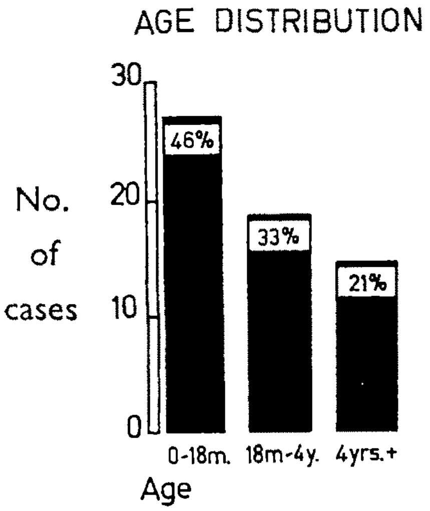

FIG. 2

ten who died, permission for autopsy was given in seven instances. In six of these, the larynx and trachea showed no more than patchy superficial abrasions with no evidence of any underlying tissue reaction. The pathologist's comment was that he had seen worse in some cases following endotracheal anaesthesia.

The seventh, a child of 6 admitted and remaining unconscious and apnoeic was artificially ventilated for three days. At post-mortem examination there was dense supraglottic and epiglottic oedema. There was subglottic diffuse haemorrhagic necrosis as far as the cricoid and there was oedema of the cords. Sub-epithelial and submucosal haemorrhages were also visible in other parts of the body. The clinical diagnosis of a fulminating septicaemia was never proven, but no other cause of death was apparent.

Experience with mechanical pulmonary ventilation indicates that there is more evidence of reaction even in survivors, than when a ventilator is not required. This reaction is possibly traumatic in nature, due to movements of the ventilator head, relative to the patient, pushing the tube up and down the larynx, as well as to the need for a reasonably well-fitting tube to give some semblance of an airtight seal. However, mechanical ventilation was used in only six cases, from which small number no firm conclusions can be drawn. Of the remaining three who died, laryngoscopy at death showed no abnormality incompatible with complete recovery.

Follow-up laryngoscopy has been refused by two parents and the appointment not kept by a number of others. Altogether, thirty-three laryngoscopies have been carried out under general anaesthesia at intervals of three and, if necessary, again at six months after the initial illness. In all except three patients the larynx was within normal limits at three months and, in these three, appearances were normal at six months—a pin-head-sized granuloma having disappeared from one or other cord in the meantime. Those who have not returned can be presumed to be functionally normal at least.

Of the 61 cases, 23 required re-intubation on one or more occasions, but were ultimately extubated satisfactorily. The remaining 28 survivors were extubated satisfactorily at the first attempt. Five cases warrant mention in some detail.

CASE 1. A big well-built boy of 9, lying unconscious with severe head injuries and multiple other injuries, had an ordinary red rubber Magill tube in place for 24 hours before changing to a Portex tube. As protective reflexes returned 4 days later, the tube was removed, but had to be repeatedly replaced for shorter or longer periods to aspirate secretions or relieve obstruction from laryngotracheal oedema and superficial slough. Tracheostomy was performed in the end, was easy to manage in such a big boy, and in this instance would have been better performed at the very beginning.

CASE 2. A boy of 7 came in with an unusually virulent and severe attack of laryngotracheobronchitis. So dense was the oedema that a Portex tube could not be pushed through the oedematous segment. Again because of his size, after establishing the diagnosis by bronchoscopy, a tracheostomy was carried out and managed without any trouble, the preliminary attempt with a Portex tube having achieved only partial relief This was the only case in the series subjected to bronchoscopy which was done to exclude some other cause for his respiratory distress in the face of persistent obstruction after intubation. It is of interest that a No. 4 Oxford tube—stiffer and tapered—gave a perfect airway for the anaesthetic for tracheostomy where the Portex tube had failed to pass.

CASE 3. Subglottic stenosis occurred in a little girl of 4 years. This child had a history of repeated attacks of croup every winter since birth, but had never had to be brought to hospital. On her first admission, however, she was severely obstructed and needed immediate relief. At 2 a.m. a misunderstanding about her age occurred. The anaesthetist understood she was 8 years old and intubated the larynx with a size 3 Portex tube (5.5 mm New British Standard). A 4.5-mm or even a 4-mm would normally have been used. This was noticed next day, but no action taken as the child seemed to be tolerating it quite well. Six days later the tube was removed, but had to be replaced within 12 hours. This time a No. 2 (5 mm) tube was used. Three days later extubation was again attempted without success, and within 24 hours the tube had to be replaced. Four days later it was again removed and after a further 4 days the child was sent home, the voice still slightly hoarse but otherwise well, for the usual follow-up.

Ten days later she was brought back apparently with a fresh attack of severe croup. Close questioning disclosed that her voice had never become completely normal in the interim. Oedema was so dense that a 3-mm Oxford tube had first to be passed as a dilator. Ultimately, a 4.5-mm Portex tube was introduced and left in position for 7 days after which it was removed uneventfully under sedation. A week later she was sent home well, although her voice was still a little hoarse.

Five days later, she was re-admitted with acute croup. Early next morning airway relief became imperative and a 4.5-mm Portex tube was passed through the nose after a preliminary dilation with a 4-mm tube. Four days later direct laryngoscopy under general anaesthetic showed a normal left cord, a granuloma anteriorly on the right cord, and very little subglottic oedema. The tube was therefore removed and remained out. In view of her previous troubles, it was decided to keep her in hospital until her voice was clear and appearances normal on direct laryngoscopy.

Ten days later when slight huskiness had been the only functional abnormality, she awoke in respiratory distress and rapidly deteriorated. Under general anaesthetic gross subglottic narrowing was observed and again a 4.5-mm tube passed after preliminary dilation with a 4-mm tube.

The lengthy comment in the case notes at this point makes it clear that a progressive subglottic stenosis rather than oedema was now unmistakably recognized. This tube was left in 1 week and 24 hours after removal laryngoscopy showed: "Both cords red and granular, trachea reddened, somewhat stenosed and showing tendency to form small areas of slough. Should have tracheostomy, and larynx rested. Suggest further laryngoscopy about 2 weeks later."

An elective tracheostomy was then performed and 4 days later at laryngoscopy ". . . the appearances are those of early cicatrical stenosis". A belated course of steroid therapy was now prescribed, but although adequate in dosage, to judge by the rapid gain in weight and other marked side effects, it had no observable effect on the progress of events. A month later at laryngoscopy ". . . the cords have returned to a virtually normal state. One cm below the glottis there is a virtually complete stenosis . . .". After a further few days of training for Mother, this little girl was sent home with a permanent tracheostomy. The present plan is to defer a definitive operation on the upper trachea and cricoid until she is older. The vocal cords and larynx itself are normal and with an adequate airway re-established in her teens she should have a normal voice. She is able to talk quite well in a whisper and should improve further when she learns to block off the tracheostomy opening with a finger for voice production.

CASE 4. This child of 7 years was convulsing repeatedly when admitted. Paralysis was induced and ventilation controlled with the help of tubocurarine and a mechanical ventilator for 36 hours, but she remained unconscious for a further 4 days with a Portex tube in position. Ten days after the initial intubation, she was regarded as well enough to permit extubation. At extubation, the trachea and larynx were observed to be coated with a tenacious slough. Culture returned a report of *Ps. pyocyanea*. She struggled along for 24 hours with moderate respiratory obstruction, but as soon as her condition began to deteriorate re-intubation was carried out and in the light of past experience with these older patients an elective tracheostomy was performed at a convenient time on the next day. A week later, the tracheostomy was decannulated without difficulty after a period of progressive corking off. She was sent home with a hoarse voice but an apparently adequate airway. She was asked to report back in a week for a check on her larynx. On her return, she was still abnormally hoarse and laryngoscopy under general anaesthesia revealed an adhesion of the cords across the tips of the vocal processes of the arytenoid cartilages. This adhesion was divided and subglottic oedema observed to be still present. A 4.5-mm Portex tube was introduced to maintain the airway and keep the adherent areas apart. She was then re-admitted to the ward. Four days later, at laryngoscopy, "Both cords are very granular and show very little movement. There is at present an adequate subglottic airway". A week later laryngoscopy showed the "tube surrounded by friable glottic granulation tissue. Cords recognizable but granular". An intercurrent attack of measles postponed the next check. Ten days later the patient found herself able to talk around the tube if she first blocked it off. It was removed next day under sedation only, and her voice improved daily thereafter. A week later laryngoscopy revealed "great improvement. Much of the granulation tissue has disappeared. There is none in the subglottic region. The cords are thickened". At the three month follow-up the voice was clear and laryngoscopy revealed a normal larynx.

CASE 5. The last case was the first in this series. A neonate, in respiratory distress from laryngeal obstruction, he had had a traditional tracheostomy performed and difficulty was experienced when attempts to decannulate were made 2 weeks later. A 3-mm tube was inserted and the tracheostomy was left to close. Difficulty in removing the Portex tube was also encountered and altogether it was reinserted 11 times. In the end we gave up trying and left him to "grow around his tube". This, in fact, is what happened and after he could be heard snuffling and coughing around his tube, it was finally removed uneventfully after a total period of 9 weeks.

DISCUSSION

The results outlined above explain why intubation has been given such a prolonged trial in this hospital. Tracheostomy carried out by the occasional surgeon (usually a medical registrar or physician) under bad conditions and with the patient often in extremis gave understandably poor results (table I). Almost half the deaths in the series could be attributed directly to the surgical complications of the operation of tracheostomy itself.

Table II shows an improvement in overall results when the operation is performed under the best conditions possible, including endotracheal general anaesthesia. In this series no deaths were attributable to the operation of tracheostomy alone, but, once established, maintenance of the patient still presented many problems. The smaller the patient the greater the difficulties.

If a hospital has an efficiently run respiratory unit in which babies and infants with tracheostomies are effectively managed with no incidence of pneumothorax or surgical emphysema, no crises due to a dislodged tracheostomy tube, and no trouble when decannulating and closing the tracheostomy, then obviously intubation has no place. This, however, has never been our experience. Tracheostomy in infants still suffers, in spite of improvements in technique and overall results, from the following complications:

Dislodging of the tube during a spasm of coughing; this may precipitate a serious emergency.
Surgical emphysema of the neck.
Surgical emphysema of the mediastinum.
Pneumothorax.
Nursing problems; the younger the patient, the less neck there is for attaching and handling the tube.
Decannulation problems.

Prolonged pernasal intubation virtually abolishes all these difficulties. The nursing staff unanimously prefer to manage, as a tracheostomy, a small stump of Portex tube projecting from the convexity of a baby's face rather than attempt to handle an insecure tube buried under the folds of the same baby's chin.

There are still troubles with decannulation, but these are never major. To re-insert an endotracheal tube is always easier than on the first occasion. To re-open a rapidly granulating and closing tracheostomy track can give rise to difficulty even in experienced hands.

The spread of infection down the tube is a problem equally common to either technique. Masks and rigid aseptic precautions on the part of all those handling the patient will minimize this, but the presence of an endotracheal foreign body which bypasses all the normal defences is a disadvantage common to both methods and demands the utmost vigilance in keeping its effects to a minimum.

Humidification is another problem common to both techniques and requires constant attention. In neonates and very small babies (under 3 months of age) the presence of the tube seems to cause minimal upset. Beyond the regular quarter-hourly instillation of fluid no further measures seem to be necessary to prevent crusting or inspissation of secretions. In the series presented here the incidence of secondary infection and of crusting in the tube was nil in babies under 3 months of age. Over the age of 3 months more active measures to humidify the inspired atmosphere are essential. The traditional steam tent has been reasonably satisfactory, but more efficient nebulizers are available and are better. The reliability, cheapness and ready availability of steam are the main reasons for its use in this series.

One incontrovertible advantage of the tube is that in a respiratory emergency it can be removed by the nurse attending the case with immediate relief of trouble. After removal of the tube there is always a brief period of a quarter to half an hour in which the airway remains clear. A baby who has dislodged his tracheostomy tube into the tissues of his neck is not always relieved by removing the tube and may be in severe straits by the time someone capable of guiding the tube back into the trachea is at hand.

As the age of the patient increases and the neck enlarges relative to the trunk and head, tracheostomy becomes progressively easier to manage and the patient's reaction to the tube appears to become progressively less favourable. Our chief difficulties have been encountered in older children.

With these older children (4 years and over), in whom tracheostomy is much less of a problem, intubation is occasionally more distressing and frightening than tracheostomy. Others tolerate the tube calmly and with understanding (fig. 3). It is reasonable with these older patients to undertake

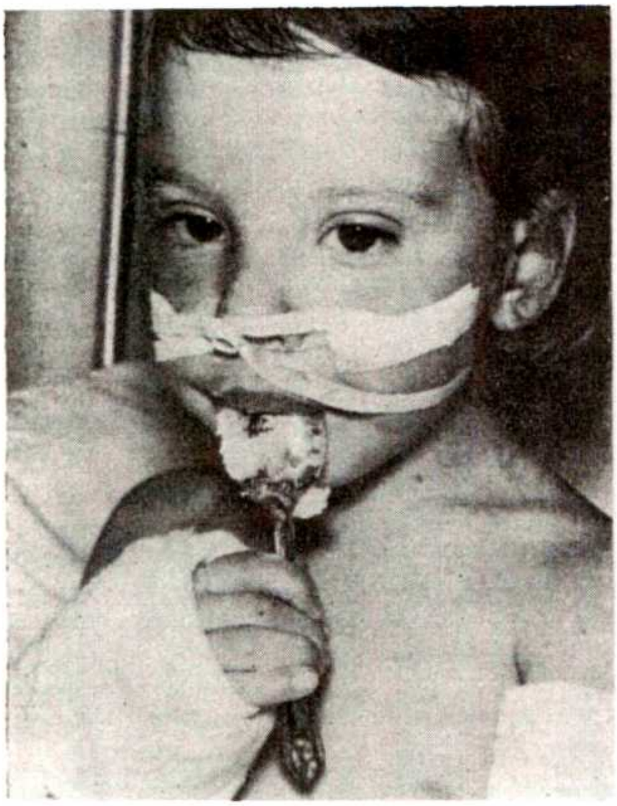

FIG. 3
Recovery phase: tube "in situ".

a trial of the tube and to proceed thence to an elective tracheostomy if such a course appears desirable or necessary.

Four cases of intubation for lower respiratory obstruction—bronchiolitis with intense bronchospasm—are cited in table III. Intubation in these four gave disappointing results. The tube, acting as a foreign body, aggravated the bronchial reaction and this was made even worse by repeated suction. There seems to be little place for prolonged intubation where the obstruction is distal to the trachea.

At this point two questions become relevant:

(*a*) Where can this technique reasonably be attempted and practised?

(*b*) Who performs the intubation?

Our reply is:

(*a*) Any institution that regularly has to manage tracheostomies in children under 5 years of age and is not satisfied with the results in this age group could reasonably give a trial to intubation with polyvinyl chloride tubes. The younger the patient the easier it is to manage the tube. Dexterity with thin strips of sticking-plaster in fixing the tube is an asset, and a loop of linen thread tied firmly to the tube at the point of egress from the nose with the loose ends fixed on either cheek by small squares of sticking-plaster averts embarrassment if the tube is inadvertently inhaled into the nasal cavity during a spasm of coughing.

(*b*) Reference to table III shows that the majority (43) of patients were in respiratory distress at intubation. For these we have used the method described. Patients in group B presented no difficulties. A suitable dose of suxamethonium, preceded or not by thiopentone according to the state of consciousness, was all that was necessary. Any anaesthetist who is competent to give an endotracheal anaesthetic for tracheostomy in any given case could reasonably attempt prolonged intubation as an alternative if he so desires.

It is felt that this technique offers: freedom from the surgical complications of tracheostomy; greater ease of nursing management; less trouble with extubation; and as already mentioned, prompt removal of the tube in emergency gives immediate temporary relief.

Whether the technique proves ultimately of value or not, two further factors deserve mention. Intubation on the spot in an emergency can then be followed by an elective tracheostomy under optimal conditions at any time during the next 24 to 36 hours. The same can be said of hospitals providing a "Flying Squad" type of emergency service. If a competent anaesthetist is on call as a member of the team, intubation on the spot followed by tracheostomy later is more practicable than emergency tracheostomy in the first instance.

The one serious complication that has occurred in this series is subglottic cicatricial stenosis of the trachea. This is a known hazard of routine tracheostomy, though nowadays rare because the surgeon knows how to prevent its occurrence. Unfortunately one cannot say yet whether tracheal stenosis is an unavoidable complication of prolonged intubation or not, as the patient in question had an oversize tube in place for 6 days without relief. In retrospect, one assumes that an ischaemic pressure necrosis of the mucous membrane lining the cricoid ring occurred, as the stenosis is in this region.

Experience in this case confirmed the already strengthening conviction that an adequate airway is the only essential factor to be constantly borne in mind. The diameter of the tube selected is, except for neonates, always one size smaller than one would normally use in routine general anaesthesia. With the older, bigger children it can quite safely be two or even three sizes smaller and still remain functionally effective.

It is our present intention to continue to use prolonged pernasal intubation as an alternative to tracheostomy until some definite and clear-cut contraindications emerge.

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INTUBATION TRACHEALE PROLONGEE CHEZ LES NOURRISSONS ET LES ENFANTS

SOMMAIRE

On présente une série de 61 cas d'intubation pernasale prolongée chez des enfants, pour des affections qui auraient autrement nécessité une trachéostomie. Une complication grave s'est produite, la sténose sous-glottique cicatricielle de la trachée, et on la discute. L'intubation pernasale prolongée a une place définie chez les enfants de moins de cinq ans, comme alternative à la trachéostomie. Le seul élément important pour réussir avec cette technique est de choisir le tube de la plus petite taille qui donne une voie aérienne silencieuse (suffisante) et un accès raisonnable pour l'aspiration des sécrétions.

LANGFRISTIGE ENDOTRACHEALE INTUBATION BEI SAUGLINGEN UND KINDERN

ZUSAMMENFASSUNG

Es wird eine Serie von 61 Fällen beschrieben, wo bei Kindern unter Bedingungen, die sonst eine Tracheotomie erfordert hätten, eine langfristige pernasale Intubation vorgenommen wurde. Es trat eine ernsthafte Komplikation auf, eine subglottische Narbenstenose der Trachea, die diskutiert wird. Bei Kindern unter fünf Jahren hat die langzeitige pernasale Intubation als Alternative zur Tracheotomie ihren festen Platz. Die wichtigste technische Vorbedingung, die erfullt werden muß, um mit dieser Methode Erfolg zu haben, ist die Wahl des kleinstmoglichen Tubus, der noch eine ruhige (angemessene) Passage der Luft zuläßt und einen vernunftigen Zugang zum Absaugen von Sekreten gewährt.

British Journal of Anaesthesia 1998; **81**: 482–487

CORRESPONDENCE

Anaesthesia for telescopic procedures in the thorax

Editor,—We read with interest the article by Plummer, Hartley and Vaughan[1] and would like to raise some points for discussion. There is increasing danger from a medico-legal viewpoint of stating in a review article that a certain course of action is "mandatory" as it might subsequently be construed that failure to perform the suggested practice is negligent. Such statements may often reflect local practice and not that of a wider body of opinion. Review articles should perhaps discuss common practice and attempt to avoid a didactic approach.

On a more specific note, mediastinoscopy certainly carries a risk of unintended vascular biopsy and an adequate venous cannula is important, but is it really "mandatory" to cannulate a leg vein in all patients presenting for mediastinoscopy, as they suggest (rather than only those patients presenting with superior vena cava obstruction)? It is common practice for our surgeons to "test" unclear areas with a fine needle before biopsy. This decreases (but does not eliminate) the risk of vascular damage.

Plummer, Hartley and Vaughan state that a reinforced tracheal tube is necessary during oesophagoscopy. There must be serious loss of attention on the part of both the anaesthetist and surgeon for the tracheal tube to be compressed by the oesophagoscope. We would suggest that proper observation and communication between medical staff should prevent the need for a reinforced tracheal tube.

Is it "mandatory" to have a CT scan before anaesthetizing a patient with a pharyngeal pouch? It may well be that the origin of the pouch has been identified with a barium swallow. What is wrong with allowing the patient to sit up on the trolley during induction of general anaesthesia?

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1. Plummer S, Hartley M, Vaughan RS. Anaesthesia for telescopic procedures in the thorax. *British Journal of Anaesthesia* 1998; **80**: 223–234.

Editor,—Thank you for the opportunity to reply to Mitchell and Shaw. We would like to comment on each of the points raised.

Where the word mandatory is used, it is used advisedly, as we believe it enhances patient safety. If the latter is the key concern, then expert witnesses and lawyers would find it very difficult to criticize.

As Mitchell and Shaw state, the classical surgical approach is aspirate first and biopsy second. They freely admit that such an action decreases, but does not eliminate, the risk of vascular damage. Yet the British and American literature state that the major complication is haemorrhage, occasionally torrential. Perhaps the testing is not that good. What cost therefore is an extra venous cannula in the leg?

We take strong exception to the third point. Classical teaching, where intubation is required for head and neck surgery, is to use a reinforced tube. The review also recommends continuous monitoring, particularly of inflation pressure. We would be interested to know how else compression of a tracheal tube could be observed. Again, why take an additional risk when it can be eliminated beforehand by using a reinforced tube?

Most surgeons would like to know where the mouth of the pharyngeal pouch is located, and inevitably would have performed a CT scan. The use of barium is acceptable but apparently somewhat old fashioned, and it tends to remain in the pouch for some time. Lastly, these patients are usually in the older age group and induction of anaesthesia in the head-up position has certain disadvantages.

Finally, one of these three original authors has been in thoracic practice for nearly 30 yr. He has followed these recommendations all his professional life and they have most certainly been instrumental in enhancing patient safety. Is anything else acceptable?

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Editor,—We read with interest the review article by Plummer, Hartley and Vaughan[1] which detailed the anaesthetic considerations of telescopic procedures in the thorax. It was a comprehensive review regarding adult patients but we were disappointed by their scant references to the paediatric population.

While some of the techniques described, such as mediastinoscopy, are seldom performed in children, others such as thoracoscopic procedures are increasingly important.[2] Oesophagoscopy, gastroscopy and bronchoscopy are also commonly indicated, yet, in discussing these, the authors have referred to children only briefly. The reader is left to assume either that there are no other problems associated with the use of the technique in this group or that the technique is not indicated in children. Furthermore, some of the authors' assertions regarding these procedures, which apply largely to the adult population, are not qualified with respect to children. In particular, the difficulties with one-lung ventilation in young children receives no mention.

With regard to thoracoscopy, there may be benefits in terms of reduced pain and decreased morbidity in children, as in adults, undergoing diagnostic procedures.[3] However, we have suggested previously that this may not be the case in operative procedures, where children may suffer considerable postoperative pain.[4] The multiple wounds associated with these procedures may approximate to the size of a thoracotomy incision in young children, and the fact that the incisions involve several sensory dermatomes makes the provision of effective postoperative analgesia more difficult. Other authors appear unconvinced of the best form of analgesia and have advocated prospective studies.[5] We found that the majority of postoperative pain was associated with the chest drain site, and thoracoscopic procedures do not necessarily decrease the duration of chest intubation in children.[6]

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Editor,—Armstrong and Martin are correct in that the article was originally commissioned for the anaesthetic management of *adult patients* for these investigations.

However, where procedures are performed in children, with the main exception of thoracoscopy, the development of both modern equipment and techniques means that the main principles set out for adults are not too far removed for those in children, except that in children they are performed under general anaesthesia.

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A case made for automated anaesthetic record keeping?

Editor,—The results of the study of Byrne, Sellen and Jones[1] made interesting reading. They questioned the accuracy of anaesthetic record charts when recording critical incidents. They observed that the more stressful the situation, the less likely the chart is to be accurate. They concluded that, "... thus, the relevance of anaesthetic chart accuracy to the legal process must be questioned." This is a well conducted study, which confirms a long standing suspicion.

What is the validity of manual record in a *res ipsa loquitur* case, where decision might rest on such record?[2] There seems to be a case to be made for automated record keeping In major emergencies such as ruptured aortic aneurysm repair, few anaesthetists would be so tenacious or perhaps paranoid enough to divide time between priorities such as rapid blood replacement and contemporaneous record keeping, until the patient is relatively stable, which may be an hour or more into surgery. It is almost inevitable that to varying degrees, such records are made up, except when there are so many anaesthetists available that it is possible to spare one for the sole purpose of accurate contemporaneous record keeping. This is now less likely.

Even protagonists of manual record keeping, who might argue that it keeps the anaesthetist in contact with the patient, might agree that in situations of mental overload the most objective recording is in the automated mode. Automated record keeping might prove to be another means of generating a spare pair of hands, in a similar way to the laryngeal mask. The claim that mental absorption and evaluation of information in the process of manual record keeping is lost during automated recording is probably no longer valid. Manual record keeping need no longer be a condition for an anaesthetist's vigilance, since the introduction of intelligent alarms technology with integrated displays.[3] Similarly, the problem of artefacts in autorecords could be solved easily by collaboration with software developers involved in the manufacture of our monitoring systems. Improved software programming should provide facilities enabling the user to mark or delete artefactual items on the record.

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Editor,—We thank Dr Adejumo for his compliments, but would like to add a note of caution. The prime purpose of our study was to measure mental workload and not to question the validity of the anaesthetic record in the courtroom. We do agree, though, that the findings lend considerable weight to the fact that such records can be of questionable accuracy, especially under conditions of high mental workload.

We do not wish to imply, however, that we are necessarily fully in favour of abandoning manual records for automated ones. Automated records have undoubted benefits For example, in two cases known to one of us (J.G.J.), failure to oxygenate the patient was documented only by the automated record. One episode led to severe hypoxaemia and a permanently disabled patient. In neither case was there any written record of oxygen saturation levels. Without the automated records, there would have been considerable speculation in court about several aspects of both cases.

However if, as seems increasingly likely, we are driven down the road of automated records, it must be emphasized that we need to pay just as much, or more, attention to validation of these records as we do to our charts. Thus systems and procedures need to be developed to ensure that automated records have *correct* dates and times, and appropriate annotation of artefacts (e.g. arterial pressure of 240/230 mm Hg during reaming in a total hip replacement). Further, we do not share Dr Adejumo's optimism that vigilance will be unaltered by the use of automated records. There is evidence in other domains[1] that automation can have negative effects on performance when systems take humans too much "out of the loop". Whether automated record-keeping in anaesthesia would have any such effects is at this point an open question.

To sum up, we feel that some work is required to better define the place of automated records. Unless we do so, there remains the possibility that they will only threaten us and benefit the plaintiffs.

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Peripheral blocks of the lower limb for repair of fractured neck of femur

Editor,—We read with interest the article on prevention of spinal anaesthesia-induced hypotension in the elderly.[1] In our opinion, there is another way to reduce hypotension in patients undergoing surgical fixation of fractured neck of femur under regional anaesthesia using a combination of lumbar and sacral plexus blocks. We describe the management of an elderly man with aortic stenosis presenting for repair of an intertrochanteric fracture

A 76-yr-old man was admitted after a fall at home. The patient had a history of tuberculosis treated by pneumothorax and mild aortic stenosis (aortic surface 0.68 cm^2, mean aortic gradient 42 mm Hg in a recent echocardiogram) associated with episodic arrhythmias. On physical examination, the patient was in moderate respiratory distress, heart rate was 125 beat min^{-1} (ECG confirmed atrial fibrillation), auscultation revealed an aortic murmur 3/6° and the lungs were clear (no clinical or radiological signs of congestive heart failure). Arterial pressure was 80/40 mm Hg. Two days later, after treatment with amiodarone, the ECG showed sinus rhythm of 85 beat min^{-1} and arterial pressure was 85/50 mm Hg. Surgery was scheduled for the afternoon.

On arrival in the anaesthetic room, arterial pressure was 97/56 mm Hg, heart rate 95 beat min^{-1} and peripheral oxygen saturation 91% breathing spontaneously, requiring oxygen 5 litre min^{-1} to increase it to 98%. After i.v. administration of alfentanil 0.25 mg, the patient was turned to the lateral position, with the fractured side uppermost. Arterial pressure decreased to 85/58 mm Hg before the blocks were inserted. Lumbar plexus block was performed according to Winnie's landmarks.[2] A 100-mm stimulating needle identified the lumbar plexus by movement of the quadriceps femoris using a stimulus less than 1.0 mA; 1.33% lidocaine 30 ml with epinephrine 1:200.000 were then injected into the lumbar plexus. Sacral plexus block was performed using the parasacral approach based on Mansour's technique[3]; 1.33% lidocaine 20 ml with epinephrine were injected after eliciting a foot plantar flexion with the help of a neurostimulator using a stimulus of 0.5–1.0 mA at 1 Hz. An iliac crest point block (lidocaine 7 ml was injected opposite an orifice located on the iliac crest) completed the analgesia effect.[4] The time to complete these blocks was 25 min. Motor block was complete in the entire fractured lower limb. The contralateral lower limb was not blocked. Surgery started 20 min after completion of the blocks. Surgery consisted of gamanail osteosynthesis performed in 28 min and was uneventful. Only 300 ml of 6% hydroxyethylstarch was required to replace blood loss and ephedrine 6 mg was added to improve haemodynamic stability without tachycardia.

The patient was fully awake and orientated throughout; further hypnotic or analgesic drugs were not given. The patient's satisfaction was measured at 95 mm using a visual analogue scale in the post-anaesthetic care unit. The patient started to walk 3 days after surgery and left hospital for a rehabilitation unit 10 days later.

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1. Buggy DJ, Power CK, Meeke R, O'Callaghan S, Moran C, O'Brien GT. Prevention of spinal anaesthesia-induced hypotension in the elderly: i.m. methoxamine or combined

hetastarch and crystalloid. *British Journal of Anaesthesia* 1998; **80**: 199–203

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4. de Visme V, Picart F, Le Jouan R, Legrand A, Savry C, Ek F. Bloc des branches perforantes latérales des nerfs sous-costal et ilio-hypogastrique *Annales Françaises d'Anesthésie et de Réanimation* 1997; **16**: 982–984.

Editor,—Thank you for the opportunity to comment on Dr de Visme's letter in which he described a case of an elderly patient with an intertrochanteric femoral fracture, whose anaesthesia was managed by a combination of unilateral regional blocks. Despite significant preoperative haemodynamic instability requiring treatment, the procedure was apparently expedited with a minimum of systemic hypotension. Dr de Visme is to be congratulated on this achievement. However, I doubt if a majority of practising anaesthetists would perform these regional techniques sufficiently regularly to maintain a high success rate and to do so within a reasonable time frame. Even in this instance, the time from commencement of blocks to surgical incision was 45 min, which I believe is longer than the average time required to instigate spinal anaesthesia (median 28 min in our data).

Moreover, this technique required a total dose of 758 mg of lidocaine with epinephrine. Although the patient's weight is not reported, it is probable that this dose exceeds the recommended maximum of 7 mg kg^{-1} for this agent, although I am aware of anecdotal reports of individuals safely administering up to 9 mg kg^{-1} of lidocaine with epinephrine. Finally, I note that ephedrine 6 mg was given to this patient, but it is not clear which haemodynamic or other criteria triggered its use.

In conclusion, while the advanced regional skills described by Dr de Visme have a place in the management of high-risk patients for femoral neck surgery in which acute afterload reduction must be minimized, it may not be feasible to expect a majority of anaesthetists to regularly practise them. Hence studies such as ours, seeking to define the optimum methods of minimizing hypotension after the more widely used technique of spinal anaesthesia must continue.

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Propofol and asepsis: is it safer to use the TCI technique?

Editor,—The recent description of accurate pharmacokinetic models for i.v. anaesthetic application has been followed by the development of the concept of a target concentration infusion (TCI). Development of a TCI model for propofol[1] and the successful correlation of predicted to real plasma concentrations[2] permitted the first patient individualized, safe, computer-assisted anaesthetic.

The propofol TCI system consists of a syringe pump (different manufacturers) incorporating TCI software[3] (Diprifusor TCI subsystem, Zeneca Ltd, Macclesfield, Cheshire, UK) and a pre-filled syringe of propofol (Diprivan, Zeneca Pharmaceuticals, Macclesfield, Cheshire, UK). Each syringe includes a coded recognition tag of specific information concerning the drug and its concentration (the programmable magnetic resonance tag) After injection of an entire pre-filled syringe, the syringe pump erases this tag.

Propofol has been associated with the risk of transmission of infection,[4] mostly as a result of not adhering to aseptic practice. Safety warnings are repeated clearly on each pre-fitted syringe ("for use in one patient only", "asepsis must be maintained" and "this syringe should not be used for drawing up any fluid"). The lock and key system of the TCI syringe pump and tagged syringe ensures the safety of the TCI technology; erasing the tag of the pre-filled syringe when it is empty enhances patient safety by preventing refilling and reuse of the same syringe.

In order to check the safety of the available TCI technology, we recovered 75 pre-filled syringe units of 1% propofol emulsion from clinical use before complete infusion of the total volume of the syringe After starting a TCI application *ex vivo* at a rate of 2 μg ml^{-1}, we noted the volume at which the message "nearly empty" appeared. The volume at which the recognition tag was erased by the syringe pump unit (Graseby 3500 incorporating Diprifusor, Graseby Medical Limited, Watford, Herts, UK) was also noted. This latter volume was defined as the volume beyond which the syringe could not be recognized successfully by the system after a short separation and replacement manoeuvre. The warning information "nearly empty" was displayed at 7.5±2.5 ml and the tag was erased at 5.0±0.5 ml.

These results imply that if separation of the pre-filled syringe from the syringe pump occurs when the message "nearly empty" appears, it does *not* impair the tag recognition capabilities. Furthermore, despite the security warning "not to be used for drawing up any fluid", it is easy to draw up the syringe, permitting the infusion of a cheaper drug while profiting from the TCI technology. Moreover, drawing up is made easy by the design of the attachment of the plastic plunger rod to the rubber stopper of the syringe as these are screwed together.

Therefore, it could be tempting to reuse pre-filled syringes, transgressing the asepsis precaution rules. Such dangerous practice has to be discouraged vigorously and newly available technology should prevent it. Despite all written warnings, we have shown that the security features of the propofol TCI system can be bypassed easily, implying that patient safety related to aseptic precautions could be improved.

We regret that the currently available Diprifusor technology does not completely prevent misuse. We believe that simple changes in the design of the plunger–stopper attachment would make such practice physically impossible.

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Ketorolac does not increase the risk of renal dysfunction after lung surgery

Editor,—The recent editorial of Myles and Power[1] raised important issues regarding the risk of postoperative renal failure induced by non-steroidal anti-inflammatory drugs (NSAID) and the most efficient methods to assess the risk–benefit ratio of perioperative administration of ketorolac, a NSAID with opioid-like potency. We agree that there is no strong scientific evidence supporting a causal link between exposure to ketorolac and subsequent renal insufficiency and that, given the low incidence of renal failure after surgery, investigations should focus on selected high-risk groups of patients or major surgical procedures, and should rely on cohort or case-control study designs.

In our institution, administration of i.v. ketorolac has been included in our multimodal pain treatment regimen for patients undergoing thoracotomy for lung resection since 1995. In addition to the standard use of i.v. or s.c. morphine and extradural local anaesthetics and/or opioids, ketorolac has been given to 151 patients at a dose of 10–30 mg tid over a median period of 2 days (range 1–4 days). In order to prevent lung oedema, we routinely limit oral and i.v. fluids for 48 h after major lung resection (pneumonectomy and double- or single lobectomy). A prospective database, including preoperative patient history, co-morbidities, laboratory results and operative and postoperative outcome data on all patients undergoing lung resection was started in March 1995 (n=234); the same items have been collected retrospectively, based on medical charts from 1990 up to February 1995 (n=269) (table 1). Among the criteria of organ dysfunction, we defined postoperative renal dysfunction as a 20% increase in plasma creatinine concentration above the preoperative value during the first 5 days after surgery. As indicated in table 1, modification of our analgesic treatment was not associated with a higher incidence of renal dysfunction (3.7% in the period 1990–94 and 2.9% in 1995–97; ns) and potential risk factors such as age, preoperative creatinine concentration, diabetes, vascular disease and duration of surgery were comparable during the two periods. Episodes of renal dysfunction were mostly transient (14/17), mild-to-moderate in nature (mean increase in plasma creatinine concentration from a mean value of 98 (SD 12) to 131 (28) mg dl^{-1}) and were associated either with increased preoperative creatinine concentrations (four of 17) and/or with other complications such as infection (eight of 17), arrhythmia (three of 17) or cardiac failure (three of 17). Only two patients receiving ketorolac (for 1 and 3 days) demonstrated transient and mild postoperative increases in serum creatinine (+25% and +31% above preoperative values).

Table 1 Characteristics of 503 consecutive patients undergoing elective thoracotomy (*n* (%) or mean (SD or range)). *P<0.05 compared with period 1990–94

	1990–94 (*n*=269)	1995–97 (*n*=234)
Postoperative renal dysfunction	10 (3.7)	7 (2.9)
Age (yr)	62 (56–70)	64 (56–72)
Preoperative creatinine (mg d^{-1})	91 (10)	93 (9)
Diabetes	17 (7)	19 (8)
Peripheral vascular disease	27 (10)	26 (11)
Duration of surgery (min)	117 (19)	122 (23)
Postoperative analgesia		
with extradural catheter	195 (72)	178 (80)
with ketorolac i.v.	0	151 (61)*

Thoracotomy represents a major surgical stress and restriction of fluid intake could further activate the renin–angiotensin–aldosterone system. Although renal blood flow is thought to be highly dependent on local prostaglandin synthesis during stressful periods, our data do not support the hypothesis that short-term administration of ketorolac impairs postoperative renal function. For the given effect size (incidence of renal dysfunction of 3.7% and 2.9%), sample sizes ($n1$=269 and $n2$=234) and alpha level (0.05, two-tailed), the statistical power of our results was 0.06; this means that the incidence of postoperative renal dysfunction was expected to be similar in the two study periods with a probability of 94%. However, several confounding factors and biases should be considered. First, this was a non-randomized observational study where two groups of patients were compared according to time periods; data were collected retrospectively from 1990 up to 1994, and prospectively thereafter. Second, extradural administration of local anaesthetics represented the mainstay of analgesic treatment in the majority of patients (72% and 80%) and blockade of renal sympathetic nerves could partly alleviate the vasoconstricting effects caused by stimulation of the renin–angiotensin system. Hence, one may question whether thoracic extradural block affords renal protection during the stressful perioperative period or whether the release of vasodilatory prostanoids (PGE$_2$, PGI$_2$) is blocked by NSAID. Third, other drugs were administered concomitantly and ketorolac was given to 61% of patients during the second period; a preoperative increase in plasma creatinine concentration and a history of gastrointestinal disorders were considered contraindications for the use of any NSAID.

In summary, we believe that ketorolac can be administered safely over a short period (2–3 days) after major surgical procedures in patients with normal renal function. Apart from results of well designed, prospective, randomized studies, analysis of local databases can guide our rational clinical decision-making.

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1. Myles PS, Power I. Does ketorolac cause postoperative renal failure: how do we assess the evidence? *British Journal of Anaesthesia* 1998; **80**: 420–421.

Editor,—We thank Licker, Höhn and Schweizer for sharing their experiences of the use of ketorolac in thoracic surgical patients. Analysis of audit data has some value in reassuring clinicians and generating new hypotheses testing. Their data demonstrated that renal dysfunction is rare after major thoracic surgery.

We wish to clarify their interpretation of the power of their observational study: a power of 6% implies a beta (type II) error of 94%. This can be re-stated as there being a 94% chance of not detecting a statistically significant difference if in fact a true difference exists. In other words, their analysis was very unlikely to demonstrate that ketorolac causes renal failure in thoracic surgical patients. As stated in our editorial, such a study would require many thousands of patients, or alternatively, studying a group of patients at much higher risk of renal failure (note: it is actually the number of end-points that determines the sample size required).[1]

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Local anaesthesia for routine ocular surgery

Editor,—I read with interest the recent article by Mawer and Coombes[1] who surveyed the current practice of local anaesthesia for routine ocular surgery by consultant anaesthetists in the Wessex region using a postal questionnaire. The survey showed that peribulbar block was the most popular block, but that retrobulbar block was also used by up to 26% of respondents. I was surprised that there was no mention of sub-Tenon's block, implying that this block is not used by this group. Sub-Tenon's block is used commonly in Aberdeen, both by anaesthetists and ophthalmic surgeons, and this spurred me into doing a literature search. While references to the technique abound in ophthalmology journals, I have been able to find only *one* reference in the anaesthetic literature.[2] It was also mentioned briefly in a review article on techniques of orbital regional anaesthesia.[3]

Sub-Tenon's block is simple and usually painless to perform; it is effective and, because of the *blunt*, specialized cannulae used to perform the block, is devoid of the potentially serious side effects of the more commonly used retrobulbar or peribulbar blocks.

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Aberdeen

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Editor,—As Dr Dark observes, it is not the current practice of Wessex anaesthetists to perform the sub-Tenon's ocular block for routine ocular surgery. Since the survey was performed, however, some anaesthetists have started to gain experience with this method of providing peribulbar anaesthesia.

It is felt that caution should be observed when the anaesthetist conducts a sub-Tenon's block. As a profession, we are unfamiliar working with scissors and forceps in such close proximity to the globe. Indeed, a globe perforation caused by scissors was reported at a recent ESA meeting. Most ophthalmologists perform this block with the aid of an operating microscope; the manual and pedal dexterity needed to operate this equipment correctly is not currently taught to trainee anaesthetists in Wessex.

Despite these reservations, we are sure that a review of the current literature, describing the method and complications of sub-Tenon's block would be well received by anaesthetists. As we indicated in our short communication, we also feel that a nationwide review of current practice of local anaesthesia for routine ocular surgery would be appropriate.

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Pain after amputation

Editor,—We were surprised to read a recent editorial "pain after amputation: is prevention better than cure?", by Thompson.[1] Thompson prompts the idea of perioperative extradural block in the prevention of phantom pain.

The almost classical study by Bach, Noreng and Tjéllden[2] is quoted in which 25 patients were allocated randomly to receive extradural bupivacaine, or morphine, or both, for 72 h before amputation (not 24 h as mentioned in the editorial) (11 patients; block group) or oral analgesia (14 patients; control group). After 6 months, all patients in the block group were pain-free, while five patients in the control group had phantom pain. The findings of Bach, Noreng and Tjéllden are supported by other studies. Jahangiri and colleagues[3] followed prospectively two groups of patients. One group (n=13) received extradural infusion of bupivacaine, clonidine and diamorphine, started 24–48 h before amputation and continued for 3 days after operation. The other group (n=11) received on demand opioid analgesia. After 1 week, 6 months and 1 yr, the incidence of phantom pain was significantly lower in the extradural group compared with the opioid group. In a preliminary study by Shug and colleagues,[4] only one of eight patients who received perioperative extradural block had phantom pain after 1 yr, whereas six of eight patients who received systemic analgesia had phantom pain. The limited validity of these studies (small sample sizes, no or insufficient randomization, and non-blinded assessment of pain) was recognized by Thompson and he called for further investigation.

In November last year we published a randomized, double-blind study[5] in which 60 patients undergoing amputation of the lower limb were allocated randomly to receive 0.25% extradural bupivacaine 4–7 ml h^{-1} and morphine 0.16–0.28 mg h^{-1} before and during operation (29 patients; block group) or extradural saline 4–7 ml h^{-1} and oral or i.m. morphine (31 patients; control group). Both groups underwent general anaesthesia for the amputation and all received extradural analgesics for postoperative pain management. Patients were interviewed about pain on the day before the amputation and about stump and phantom pain after 1 week, and 3, 6 and 12 months. Blindness during the study was ensured by two independent examiners. Study end-points were rate of stump and phantom pain, intensity of stump and phantom pain, and consumption of opioids.

Median duration of preoperative extradural block (block group) was 18 h and median duration of postoperative extradural pain treatment (both groups), 166 h. After 1 week, 14 (52%) patients in the block group and 15 (56%) in the control group had phantom pain. The values for the block *vs* control group were: 14 (82%) *vs* 10 at 3 months; 13 (81%) *vs* 11 at 6 months; and 9 (75%) *vs* 11 at 12 months. Intensity of stump and phantom pain, and consumption of opioids were also similar in the two groups at all four postoperative interviews. Thus we were not able to confirm the findings of the previous studies.[2–4] In addition, we showed that preoperative extradural block had no effect on post-amputation allodynia and wind-up-like pain.[6] These findings suggest that although sensitization plays a role in persistent pain, it is not possible to prevent classical aspects of sensitization by transient extradural block.

While extradural pain treatment may be efficient in reducing preoperative ischaemic pain and postoperative stump pain, perioperative extradural block started 18 h before amputation and continued into the postoperative period does not prevent phantom or stump pain.

Thompson is correct when he states that the use of extradural infusions is not without risk. Extradural infections must be taken into account, especially among amputees who often have infected ulcers and diabetes. Extradural catheters should not be placed with the purpose of preventing phantom pain.

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Editor,—Thank you for the opportunity to reply to Nikolajsen and colleagues. Their study[1] was not available when the editorial[2] was written. Those interested in the subject will read the editorial in the context of current available evidence, including that from Nikolajsen and colleagues.

Does their single study provide the definitive answer to the question of prevention of pain after amputation? There has already been discussion in the literature regarding this issue. In a commentary that accompanied Nikolajsen and colleagues' study, Katz[3] recognized the value of this work. However, in view of the complexity that surrounds the subject of post-amputation pain, he called for further high calibre research to be done. McQuay, Moore and Kalso,[4] in the subsequent correspondence, contested this notion.

How much evidence is required to provide adequate proof? Before dismissing the possibility of prevention of pain after amputation, the best evidence must be sought because for some prospective amputees the future is grim. Such best evidence should come from a body of literature of good quality and consistency from which a strong recommendation can be made on the appropriate course of action. In my view, such a body of literature does not yet exist and although the work of Nikolajsen and colleagues is an important contribution, it does not in itself provide the definitive answer.

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Stature of anaesthetic personnel and positioning of patients

Editor,—I read with interest Dr Heath's editorial on some of the problems the more "vertically challenged" anaesthetist or anaesthetic assistant may face.[1] Coming from the other side of the normal distribution (I am 197 cm tall), I feel that some important points were overlooked and deserve to be highlighted.

I have worked in operating theatres where I regularly banged my head on the operating light (or, in the case of one particular theatre, the anaesthetic gas pod suspended from the ceiling!), because the highest it could be raised was to the middle of my forehead. I prefer to perform tracheal intubation with the operating table raised above its lowest point; in the case of rapid sequence induction, I often cannot do this as my assistant may not be tall enough to apply cricoid pressure correctly in my preferred intubating position. The end result is regular lower backache at the end of the working day. Similarly, standing up stretching to try to hold a mask on a patient's face while bagging from a Bain circuit situated less than 1 m from the floor does not help one's lower back.

More attention should be placed on the ergonomics and design of operating theatres and anaesthetic equipment. In addition to tables which can be adjusted up and down thus helping with proper patient positioning, bagging circuits which can be elevated or lowered and theatre lights which can be retracted correctly would surely help reduce long-term morbidity among anaesthetic personnel

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Editor,—Dr McCourt's experience usefully extends recognition of the operating theatre as a hazardous environment for staff and patients I would prefer to translate his passive tense, "more attention should be placed ..." into an active, "anaesthetists should actively involve themselves in the design of theatres and equipment, paying due attention to ergonomics". Current training ensures that anaesthetists are exposed to all surgical specialties and are thus best placed to appreciate the needs of all medical staff within the operating theatre.

I hope that my editorial has suggested the solution to at least one of Dr McCourt's problems: standing his assistant on one or more platforms should allow effective cricoid pressure with the patient at his preferred height. With regard to the other, why not sit down? Many irksome problems are regarded as too mundane for attention. Simple solutions may be identified if they are focused upon.

M. L. Heath
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Vecuronium, like rocuronium, causes pain on injection

Editor,—In their short communication, Borgeat and Kwiatkowski stated that "vecuronium has not been associated with pain on injection."[1] But in our practice, we have noticed that vecuronium given before induction of anaesthesia frequently causes pain on injection. This phenomenon has been reported previously[2,3]

It is believed that vecuronium causes pain on injection as a result of its low pH. Rocuronium has approximately the same pH as vecuronium, and probably causes pain by the same mechanism. We disagree with the conclusion of the authors that "the absence of pain in patients receiving 0.9% NaCl 1 ml adjusted to pH 4" argues against low pH as the mechanism of pain. This conclusion was based on only five patients, risking a type II statistical error. Furthermore, other acidic agents are known to cause pain on injection.[4]

We also noted that the incidence of severe pain on injection of rocuronium, as reported by the authors, was much higher than in a previous study (80% *vs* 12%).[5] Unfortunately, the authors did not offer any explanation for this difference. They administered the agents in random order, saline 1 ml and rocuronium 1 ml, 30 s apart, in the presence of "venous stasis". This can result in an increase in the osmolality of the mixture in the vein. Increased osmolality is known to cause increase in pain on injection with vecuronium[3] and other drugs.[4] Furthermore, factors such as local distension of the vein, reduction of buffering by flowing blood and longer exposure time of rocuronium to the vessel wall are encouraged by stasis. These factors have been associated with an increase in pain on injection of propofol, and may have a similar relevance for rocuronium.[6] We postulate that these factors were responsible for the high incidence of severe pain on injection of rocuronium

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British Journal of Anaesthesia 1998; **81**: 488–489

BOOK REVIEWS

Problems in Anaesthesia. Pre-operative Evaluation in an Era of Cost Containment, vol. 9, No. 2. L. A. Fleisher (editor). Published by Lippincott-Raven, Philadelphia. Pp. 270; indexed; illustrated. Price US $127.00.

This is a North American book and problems encountered in the USA have a habit of crossing the Atlantic. Certainly most British anaesthetists will sympathize with a remark in the preface "Once, an anesthesiologist could see the patient the night before surgery and reflect leisurely on the elements of the case." The aim of this book is to show how to maintain good quality anaesthesia in a world of increasing financial pressure.

The American perspective leads to concepts which seem common sense to the British reader. For example, the scheme for assessing the cardiac patient advocates moving away from blanket investigation towards clinical screening. The importance of exercise tolerance and the proposed surgery is emphasized. But the point is well made that preoperative tests should not be carried out unless they change anaesthetic management. Various scoring systems are offered to assess exercise tolerance. Golfers will be disappointed to learn that their sport rates only 4 metabolic equivalents, while football and singles tennis score >10.

The chapter on cardiac assessment is mirrored by most of the other chapters which take a systematic approach. While each contains a commendably thorough discussion of perioperative management, there is a paucity of evidence for the cost effectiveness of any intervention, largely as a result of the absence of controlled studies. The recommendation to investigate patients only after thorough clinical assessment occurs repeatedly. Unfortunately, this will have little impact on reducing perioperative cost in the UK and Northern Ireland.

Some recommendations have a decidedly non-cost effective ring to British ears. If a patient with a goitre has tracheal narrowing on chest x-ray, CT scanning is advocated to help predict the maximal size of the tracheal tube that will pass without difficulty.

The chapters on outpatient surgery and preoperative assessment clinics give an interesting insight into the approach to the rapid increase in day-case surgery in Stanford Hospital. There are some interesting insights, including the necessity to document savings produced by changes in practice to justify those changes to hospital managers.

The chapter on assessment of children describes some innovative approaches to avoid poor evaluation and "frustration for the anesthesiologist and surgeon ... and anger on the parents' part." These include telephone screening.

This book has been painstakingly researched and referenced. To discover published evidence that ondansetron reduces feelings of paranoia in Parkinsonian patients receiving high doses of levodopa is exemplary. On the whole, the book is well produced, although some diagrams and tables are too small As a review of perioperative management of the surgical patient, this is a good book; but for British readers at least, it will be little help in reducing costs while maintaining standards of care. However, it serves as a useful reminder that blind screening is a poor substitute for careful patient assessment.

A. G. Jones

The Laryngeal Mask Airway: A Review and Practical Guide. J. R. Brimacombe, A. I. J. Brain and A. M. Berry (editors). Published by WB Saunders, London. Pp. 300; indexed; illustrated

The foreword, written by Jonathan Benumof, sets the scene regarding the content and presentation of this small but well written book. It is also interesting to note that the Americans were very late in introducing the LMA into clinical practice.

The anatomy is mainly applied and discusses correct placement of the LMA, with particular reference to the cricoid and cricoid pressure. However, the reader may become aware of bias in favour of one author's view. The physiology is a record of what is accepted wisdom and reflects that insertion of the LMA does not produce too many changes under normal conditions.

The device details are interesting and examine what is currently available, ending with a cost effective commentary This is followed by a well written section on preparation for use which is particularly well illustrated.

Anaesthetic managements using an LMA, highlighting both the advantages and disadvantages, is well written. It is followed by an honest appraisal of possible problems, particularly complications and important recommendations to avoid the transfer of infection. There is an attempt to justify the use of an LMA in all manners of advanced surgical procedures, some of which I would strongly oppose, particularly in major procedures.

The crunch chapter is the one on the difficult airway. It is very comprehensive, well balanced, easy to read and understand. It has a wealth of references to support what is written. This chapter should be essential reading for both trainees and consultants.

The non-anaesthetic uses are interesting, but realistically it is the use of the LMA in resuscitation that is important both in hospitals and in the field. To some extent this philosophy is continued in the chapter on paediatrics. Although its use in paediatric anaesthesia is increasing, it has not yet replaced the tracheal tube.

The proposed modifications and future uses of the LMA are interesting but whether increased research and development costs will produce a generally more efficient piece of apparatus is debatable, particularly given the parlous state of health resources.

The last chapter, entitled quick references, summarizes in an easily readable fashion everything from trouble shooting and clinical investigations to techniques.

The small book is well written, well illustrated and comprehensively referenced. It is somewhat historical in nature but affords some glimpses into the future. Nevertheless, it is well worth reading if only for the chapter on the anaesthetist's nightmare, the unpredicted and difficult airway. I would not recommend personal purchase but would urge each anaesthetic library to have a copy

R. S. Vaughan

International Anesthesiology Clinics: Endocrine Disorders and Anaesthesia. J. Desborough (editor). Published by Lippincott-Raven, Philadelphia. Pp. 164; indexed; illustrated.

This text is one of the *International Anesthesiology Clinics* series and deals with endocrine disorders which are commonly encountered in anaesthesia or encountered more rarely but present specific problems for anaesthesia. The authors are all from the UK, mainly around London. The book consists of eight chapters. The first deals with the physiology of the endocrine system, while the subsequent six chapters cover anaesthesia for pituitary tumours, diabetes mellitus, parathyroid disease, adrenocortical disorders, phaeochromocytoma and carcinoid, respectively. The final chapter deals specifically with endocrine problems during pregnancy.

The chapter on the physiology of the endocrine system has a clear explanation of the classifications, mechanisms of actions and control of hormones and their secretion, followed by a brief outline of the physiology of the common disorders associated with the major endocrine organs. Subsequent chapters on anaesthesia for disorders of the various organs follow a general pattern; starting with the pathophysiology of the organ, diagnosis of the disorder and clinical presentation of the disease. Anaesthesia is then dealt with in the standard manner of preoperative preparation, induction, maintenance, monitoring and postoperative care. The majority end with special situations, such as anaesthesia in pregnancy or different surgical techniques, such as laparoscopy for phaeochromocytoma. In general, these are good, comprehensive reviews of the literature relating to the diagnosis of the various diseases and their anaesthetic management. In particular, the chapters dealing with thyroid disease, phaeochromocytoma and carcinoid are very clear. The chapter on diabetes contains a lot of information but I found it less well structured than the other chapters. The chapter on endocrine problems during pregnancy deals mainly with thyroid and pituitary diseases but also has a short section on the adrenals.

I found this an interesting book to read with plenty of useful information on problems that are commonly encountered, such as diabetes and thyroid disease, and a useful reference text for those which are encountered more rarely, such as phaeochromocytoma and carcinoid. Overall, it is well written and comprehensively referenced.

I think that this book will provide a useful reference text for a departmental library and will also be a useful source of information for those preparing for anaesthesia examinations.

C. S. Reilly

Neural Blockade, 3rd Edn. M. J. COUSINS AND P. O. BRIDENBAUGH (editors). Published by Lippincott-Raven, Philadelphia. Pp. 1177; indexed; illustrated. Price £97.75.

The third edition of *Neural Blockade* has been eagerly anticipated by all those who have an interest in regional anaesthesia and pain management. The second edition (1988) earned an international reputation and was described as a "blockbuster". It would not have been sufficient to revise what has already been written because so much has happened in the past 10 years. Cousins and Bridenbaugh have not disappointed with this new edition. The introduction of 28 new authors has added a freshness to this authoritative textbook. The third edition has almost the same page numbers as its predecessor, but an increase in page size to the standard A4 (US) layout increases the content by approximately 20% and also means it will sit neatly beside recent volumes of the popular anaesthetic journals.

The editors have succeeded in drawing together 52 authors from 10 different countries, nine of whom are European, with minimal repetition. All the authors are well known in the field of regional anaesthesia and pain management for their research expertise and communication skills. It is pleasing to see the contributions made by the late John Bonica, Ben Covino and Terry Murphy included because of their particular skills which we all enjoyed before their untimely deaths. The chapters are all well illustrated with full references and the emphasis on evidence based medicine is quickly apparent. This is not a book of opinion but of carefully argued evidence. The prize for the most references goes to Tony Yaksh with 881 references in his chapter on the physiologic and pharmacologic substrates of nociception and nerve injury.

The book is clearly divided into three parts: pharmacology and physiology; techniques; and pain management. A foretaste of what is to come is experienced in the first chapter on history, which is a joy to read, and is well illustrated with good quality photographs. Historians will be delighted to see 143 references to original works dating back to 1784. The contributions on physiology and pharmacology are excellent; complex issues are presented in a concise and easily understandable manner, with clear diagrams and summary tables. Henrik Kehlet's chapter on modification of responses to surgery is up to his usual very high standard, although his reference list deviates from the norm found in the rest of the book.

Part 2, techniques of neural blockade, is divided into familiar subsections, although it was a little confusing to find obstetric and gynaecologic surgery listed under head and neck! The individual categories of technique are extremely well written by experts in their field. More emphasis could have been placed on the use of regional anaesthesia in trauma, the risks of compartment syndrome and the use of magnetic resonance imaging in the diagnosis of spinal haematoma.

The case reports within Terry Murphy's chapter on somatic blockade of head and neck are most enjoyable, particularly his pointed comment about rugby forwards. The chapter on neural blockade for ophthalmic surgery describes peribulbar block by superonasal and inferotemporal transcutaneous injections. This has largely been superseded by a single medial orbital transconjunctival injection, at least in the UK.

The chapter on obstetric and gynaecologic surgery is a collaboration between Australia and North America and succeeds in presenting an up-to-date international review which has 640 references. The chapter on complications of neurolytic neural blockade is comprehensive but is strangely out of place in part 2 and more logically would have been placed after the chapter on techniques of neurolytic neural blockade in part 3.

The third part has three new chapters and reflects the massive development in our understanding of pain mechanisms and advances in pain management. This section contains much new information which all clinicians practising in the field of acute and chronic pain management will find of great interest. The psychology of pain is not forgotten and receives full emphasis by Ronald Melzack. Acute pain management, acute pain services, the evolution of pain medicine and the multidisciplinary approach to pain are all covered fully. There are two chapters which point the way to the future and make fascinating reading. The cloning of drug receptors and the ability to block ion channels in excitable tissue with a wide variety of drugs promises significant advance in our treatment of pain as we progress towards the new millennium. The book finishes with a look into the future in an essay by Patrick Wall entitled, "New horizons". Professor Wall worries about the validity of his predictions but who else is better qualified to make them I was delighted to read his criticism of the direction of current science towards reductionism. Molecular biology does not exist in isolation, it does not provide the ultimate answer because the biological system within which molecules exist must be understood also. We hear that transplantation of cloned cells which release neurotransmitters or encourage neural healing is the great hope for the future. Perhaps the next edition of this book will be entitled "Neural manipulation".

This book is excellent reading It is three very high quality books presented as one. It is essential reading for the basic scientist, the clinical researcher and the clinician, because it presents the "whole picture" from which we must step back and appreciate in its entirety at regular intervals. The editors and authors should be congratulated as the third edition surpasses its predecessor and graduates from "blockbuster" to masterpiece.

J. H. McClure

Post-operative Recovery and Pain Relief. R. ELTRINGHAM, W. CASEY AND M. DURKIN. Published by Springer, Berlin. Pp. 199, indexed; illustrated. Price £29.50. ISBN 3-540-76078-4.

Currently, patients undergo a widening spectrum of surgical and anaesthetic procedures, on a background of an increasing complexity of concomitant medical disease. Staff providing continuing medical and nursing care in the immediate postoperative period have to deal efficiently and safely with the hazards of a sudden precipitous deterioration in a patient's condition, and the many other clinical problems that accompany this patient population. Early recognition of problems, and provision of effective analgesia in keeping with rising national standards, demand high levels of vigilance, practical skills and knowledge. This well referenced book goes some considerable way towards providing the reader with a good initial overview and an easy reference source of the problems encountered in the recovery (post-anaesthetic care) unit.

The book begins with two chapters on recovery unit design, equipment, safety issues and the progress of normal recovery. The scope of subsequent chapters encompasses standard and advanced monitoring, and a range of clinical problems during recovery from specific operations. Individual chapters are devoted to analgesia, coexisting medical disease and day surgery. The information is packaged in a concise, easily readable form, with the aid of frequent, easily understandable diagrams, including a range of cardiac dysrhythmias. A number of tables detailing information such as maintenance i.v. fluid requirements and ASA classification, and sample observation charts for patient-controlled and extradural analgesia are also included. An appendix of drug doses commonly used, and some translations of a handful of standard recovery phrases, concluded this useful book.

Text size and layout make this a very readable book, and there is adequate space for additional notes. A section on common critical incidents in the recovery unit would have been interesting. Although the recently updated European Resuscitation Council guidelines are not covered, overall this book is a clear and practical starting point for staff less familiar with everyday and complex early postoperative clinical problems. Key practical information is an underlying theme throughout.

This book should appeal mainly to both trainee anaesthetists and all grades of other staff in the recovery unit, in addition to nursing and junior medical staff providing postoperative care on the general surgical ward or high dependency unit. It is a useful addition to a departmental or individual bookshelf, whose content will remain relevant for future patient populations in the coming millennium.

P. Mullen

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